# EXECUTIVE SUMMARY AND CONCLUSIONS FOR PHARMACOLOGY/TOXICOLOGY

# NDA 20-998 CELECOXIB (CELEBREX™)

## SUMMARY:

### 1. PHARMACOLOGY/PHARMACODYNAMICS

*1.1. ACTION-RELATED PHARMACOLOGY*

SC-58635 was demonstrated to have following properties.

1.1.1.In Vitro -

SC-58635 preferentially inhibited COX-2 mediated $PGE_2$ production by human whole blood and dog whole blood.

1.1.2. *In Vivo* -

- Anti-inflammatory Activity - SC58635 was effective in the following animal models.
  (1) carrageenan-induced rat paw edema model with an $ED_{50}$ value of $7 \pm 1$ mg/kg;
  (2) adjuvant induced arthritis in rats by the inhibition of cartilage destruction, bone lysis, bone proliferation, soft tissues edema and synovial iflammation with an $ED_{50}$ value of $0.3 \pm 0.1$ mg/kg; and
  (3) carrageenan-induced air pouch in rats by the inhibition of $PGE_2$ and 6-keto $PGE_{1\alpha}$ with an $ED_{50}$ value of $0.2 \pm 0.1$ mg/kg.
- Analgesic Activity - SC58635 was effective in the following animal models.
  (1) Hargreaves' hyperalgesia model with an $ED_{50}$ value of 0.35 mg/kg;
  (2) formalin induced hyperalgesia in the mose hindpaw model;
  (3) pheyl-benzoquinone induced doxoflexion in mice; and
  (4) acetic acid-induced writhing in mice.
- Anti-pyretic Activity - SC58635 was shown to reduce LPS-induced fever but did not alter normal temperature in rats.
- Chemoprevention Properties - Reports indicated that administration of SC58635 in the diet to rats at 1500 ppm inhibit azoxymethan-induced colonic aberrant cryptic foci and tumors. Reports show that NSAIDs use in the general population is associated with a reduced risk (40-50%) of colon cancer death[1]. It has been demonstrated that colorectal tumors have elevated levels of COX-2[2,3]. The mechanism of chemoprevention by NSAIDs is not clear. However, NSAIDs induced apoptosis in human colorectal cancer cells has been demonstrated[4].



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1 Thun, MJ, 1995. Gastroenterol Clin North Am. 25: 333-348.
2 Tsujii, M. and Bubois, RN, 1995. Cell 83: 493-501
3 Morin, PJ, Vogelstein, B and Kinzler, KW, 1996. Proc. Natl. Acad. Sci. USA 93: 7950-4820.
4 Chan, TA, et al., 1998. Proc. Natl. Acad. Sci. USA 95: 681-686.

*2.3. CARCINOGENICITY*

The carcinogenic potentials of SC-58635 were accessed in rats and mice.

**Rat Study** - Groups of rats were given SC-58635 in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 as a suspension once daily by oral gavage at a dose schedule as shown in the following table for 104 weeks.

| Group | Dose mg/kg/day | | | | |
|---|---|---|---|---|---|
| | Wk 1-17 | Wk 18-77 | | Wk 78-104 | |
| | ♂ & ♀ | ♂ | ♀ | ♂ | ♀ |
| 1 (Control) | 0 | 0 | 0 | 0 | 0 |
| 2 (Low) | 20 | 20 | 20 | 20 | 5 |
| 3 (Mid) | 80 | 80 | 80 | 80 | 10 |
| 4 (High) | 400 | 400 | 200 | 200 | 200 |



The doses selected in this study were based on the results of a 4-week oral gavage study at doses of 0, 20, 80, 400 and 600 mg/kg in which it was shown that absorption of SC-58635 attained a plateau at dosages ≥400 mg/kg/day for ♂ rats and deaths were seen at 600 mg/kg/day for ♀ rats. Based on GI (necrosis/perforation/inflammation with secondary peritonitis) and kidney (pyelonephritis, ♂ only) toxicity findings as well as mortality observed in this study, MTD was reached for both ♂ and ♀. There was no treatment-induced increases in the tumor incidence rates. The exposure to SC-58635 in the high dose ♀ rats, as measure by $AUC_{0-24}$ was ~20 and 10x of that observed in humans at the doses of 200 and 400 mg/day, respectively. The exposure of the high dose ♂ rats to SC-58635, was ~10 and 5x of that observed in humans at 200 and 400 mg/day, respectively. The NOAEL for ♂ was 20 mg/kg and was not perceptible for ♀.

**Mouse Study** - Groups of mice were given celecoxib at the doses shown in the following table via dietary admix.

| Group | Dose (mg/kg) | | | | |
|---|---|---|---|---|---|
| | ♂ | | ♀ | | |
| | Wk1-18 | Wk 19-104 | Wk1-18 | Wk19-22 | Wk 23-104 |
| N | 0[a] | 0 | 0 | 0 | 0 |
| 1 | 25 | 12.5 | 50 | 25 | 25 |
| 2 | 50 | 25 | 100 | 50 | 50 |
| 3 | 75 | 37.5 | 150 | 75 | 150 |



The doses selected in this study were based on toxicity findings of a 13-week dietary admix (♂: 0, 75, 150 and 300 mg/kg; ♀: 0, 150, 300 and 1000 mg/kg). Due to excessive toxicity, high dose group (♂ and ♀) was terminated at Week 80. Treatment-caused histopathological changes were limited to the GI tract (erosion/ulceration with associated chronic active inflammation in the glandular stomach, duodenum, jejunum, ileum, cecum, and colon at one or more sites). Low incidence of pyelonephritis was noted in the ♂ mice. The GI injury was the most common cause of death in high-dose animals. Therefore, the MTD was reached. No treatment-induced increases in the tumor incidence rates were identified. The exposure to SC-58635 in the high dose ♂ and ♀ mince was equivalent to ~2-3x of values seen in humans (200 or 400 mg/day). The NOAEL for either ♂ or ♀ could not be determined for this study as treatment-induced toxicity was observed in all SC-58635 treated groups.

## 2.4. REPRODUCTIVE TOXICOLOGY

The following table summarizes the effects of SC-58635 on fertility, reproductive functions, embryo-fetal development, and peri-/post-natal development.

| Animals Species | Dose (mg/kg) | Duration of Treatment | Observations | NOAEL (mg/kg) |
|---|---|---|---|---|
| **FERTILITY, EARLY EMBRYONIC DEVELOPMENT→IMPLANTATION** | | | | |
| ♂ & ♀ Rats Crl:CD®(SD)BR | 0, 60, 300, 600 | ♂: ≥28 days prior to mating → the end of study<br>♀: 14 day prior to mating→Gestation Day 7 | ≥ 60 mg/kg: ↓ live fetuses and implantation sites; ↑ preimplantation loss. | ♂: 600<br>♀: <60 |
| ♀ Rats Crl:CD®(SD)BR | 0, 15, 30, 50, 300 | 14-day prior to mating→Gestation Day 7 | ≥50 mg/kg: ↓ live fetuses and implantation sites; ↑ pre- and post-implantation loss.<br>300 mg/kg: ↓ corpora lutea | 30 |
| ♀ Rats Crl:CD®(SD)BR | 0, 60, 300 | 14-day followed by a 14-day reversal period before mating | No effects. | 300 |
| **TERATOLOGY- EMBRYO-FETAL DEVELOPMENT** | | | | |
| ♀ CD Rats VAF | 0, 10, 30, 100 | Gestation Days 6→17 | 100 mg/kg: slight ↓ live fetuses.<br>≥30 mg/kg: ↑ incidence of wavy ribs | 30 |
| ♀ Rats Crl:CD®(SD)BR | 0, 10, 30, 100 | Gestation Days 6→17 | ≥30 mg/kg: ↑ incidence of diaphragmatic hernia, 5th sternebrae incomplete ossification | 10 |
| ♀ Rabbits Hra: (NZW)SPF | 0, 6, 30, 60, 300, 600 | Gestation Days 7→18 | 600 mg/kg: ↓ body weights and food intake; ↑post-implantation loss; ↓ live fetuses. | 300 |
| ♀ Rabbits Hra: (NZW)SPF | 200, 400, 600 | Gestation Days 19/21→23/25 | 600 mg/kg: ↓ body weights (5%) | 600 (?) |
| ♀ Rabbits Hra: (NZW)SPF | 0, 60, 150, 300 | Gestation Days 7→18 | ≥150 mg/kg: slight ↑ sternebrae fused and sternebrae misshapen<br>300 mg/kg: slight ↑ rib fused; ↑ post-implantation loss; ↓ live fetuses. | 60 |
| **PERINATAL/POST NATAL DEVELOPMENT** | | | | |
| ♀ Rats Crl:CD®(SD)BR | 0, 10, 30, 100 | Gestation Day 6→Days 21-23 post partum | $F_0$ -<br>≥30 mg/kg: Deaths or Moribund (1 @ 30, 8 @ 100 mg/kg) with GI lesions; transient ↓ in food consumption (Gestation Days 6-9); ↓ live pups; ↑ dead pups.<br>$F_1$ & $F_2$ - Normal. | 10 |

A comparison of exposure to SC-56835 on the last day of dosing in rat and rabbit reproductive study to human clinical exposure is presented in the following table.

| Species | NOEL (mg/kg) | Exposure in Animal | | Ratio of Animal Exposure/Human Exposure to SC-58635 | | | |
|---|---|---|---|---|---|---|---|
| | | | | 200 mg/day[a] | | 400 mg/day[a] | |
| | | $C_{max}$ (μg/ml) | $AUC_{0-24}$ (μg•hr/ml) | $C_{max}$ | $AUC_{0-24hr}$ | $C_{max}$ | $AUC_{0-24}$ |
| **Embryo-Fetal Developmental** | | | | | | | |
| Rat | 10 | 3.20 | 47.6 | 4.7 | 5.7 | 2.4 | 2.8 |
| Rabbit | 60 | 2.37 | 41.5 | 3.5 | 4.9 | 1.8 | 2.5 |
| **Pre-Mating and Early Pregnancy** | | | | | | | |
| Rat | 30 | 5.17 | 63.3 | 7.7 | 7.5 | 3.8 | 3.8 |

[a] The mean $C_{max}$ and $AUC_{0-24}$ values for the 200 mg/day dose were 0.675 μg/ml and 8.40 μg•hr/ml, respectively and the mean $C_{max}$ and $AUC_{0-24}$ values for the 400 mg/day dose were 1.35 μg/ml and 16.8 μg•hr/ml, respectively. Ratio was calculated by dividing animal Day last $AUC_{0-24hr}$ or $C_{max}$ values by respective human values.

## 2.5. *GENETIC TOXICOLOGY*

The mutagenic potentials of celecoxib were evaluated in both *in vitro* and *in vivo* systems and results are summarized in the following table.

| Assay System | Indicator Cells | SC-58635 Conc. | Findings |
|---|---|---|---|
| Ames | *Salmonella typhimurim* strains (histidine auxotrophs) TA97a, TA98, TA100, TA1535 and TA1538 | 10, 50, 100, 500, 1000, and 5000 μg/plate | Toxic at concentrations of ≥500 μg/plate<br>Not mutagenic at concentrations up to 500 μg/plate |
| CHO/HGRT Mutation | CHO cells (subline K1-BH4) | Range-Finding: μg/ml<br>-S9: 4, 8, 12, and 16 μg/ml<br>+S9: 15, 30, 45, and 60 μg/ml | Not mutagenic at doses up to 16 μg/ml and 45 μg/ml in the absence and presence of S9 activation, respectively. |
| Chromosome Aberration | CHO-WBL cells | Range-Finding: μg/ml<br>-/+ S9: 10, 20, and 40 μg/ml | +S9: ↑ frequency in cell endoreduplication.<br>Slight but not significant ↑ in % cells with aberration. |
| Micronucleus Assay | ♂ & ♀ Crl:CD®(SD)BR Rats - Bone Marrow Cells | 150, 300, and 600 mg/kg/day po for 3 days | Not clastogenic |

## 2.6. *SPECIAL TOXICOLOGY*

The antigenic properties and the potentials to cause skin sensitivity, dermal or ocular irritations of celecoxib were evaluated and the observations are summarized in the following table.

| Testing System | Species | SC-58635 (Dose/Route) | Observations/Comments |
|---|---|---|---|
| **ANTIGENIC PROPERTY** | | | |
| ASA, HmPCA (4 hr), and HtPCA Rxns[a] | ♂ Guinea Pigs | Sensitization: 5, 25 po or 25 mg/kg sc<br>Challenge: 5 mg/kg iv | Not antigenic. |
| **SKIN CONTACT SENSITIVITY/DERMAL/OCULAR IRRITATION** | | | |
| Guinea Pig Maximization Test | Crl:(HA)BR Albino Guinea Pigs | Sensitization: 5% in FCA/$H_2O$ id[b]<br>Induction and Challenge 25% in Petrolatum dermal topical | **No concurrent + control was performed. Therefore, the study was not valid.** |
| Primary Skin Irritation | ♂ Hra:(NZW)SPF Rabbits | 0.5 g dermal occlusion | No dermal irritation. |
| Primary Eye Irritation | ♂ Hra:(NZW)SPF Rabbits | 0.011 g (0.1 ml wt equivalent) lower everted eye lid | Minimal ocular irritation. |

[a] ASA = Active Systemic Anaphylaxis; HmPCA = Homologous Passive Cutaneous Anaphylaxis; HtPCA = Heterologous Passive Cutaneous Anaphylaxis; Rxns = Reactions.

[b] FCA = Freund's Complete Adjuvant; id = intradermal injection

### 2.7. TOXICITY RELATED TO THE STATING MATERIAL (SC-70986, 4-SULFONAMIDOPHENYL HYDRAZINE HYDROCHLORIDE) FOR SYNTHESIS OF SC-58635

The following table shows the summary of toxicological findings for the stating material (SC-70986, 4-sulfonamidophenyl hydrazine hydrochloride) in various studies.

| Testing System | Species/Indicator | SC-70986 Dose/Route | Findings |
|---|---|---|---|
| Acute Toxicity | ♂ & ♀ Rats Crl:CD®(SD)BR | 250, 500, 1000, and 2000 mg/kg/ ml po | $LD_{50}$: ♂, 1000 (558-1792); ♀, 707 (483-1036). Clinical Signs: Hyporeactivity, staggered gait, absence of gasping/righting reflex, prostration, clonic convulsions, thin appearance, hunched posture, red-stained face, excessive salivation, lacrimation, mydriasis, dyspnea, soft stool, wet and/or yellow-stained urogenital area |
| Primary Eye Irritation | Rabbits Hra:(NZW) SPF | 73 mg lower eyelid | Unflashed: corneal and iridal involvement and moderate conjunctival irritation. Flushed: corneal involvement and slight conjunctival irritation. |
| Primary Dermal Irritation | Rabbits Hra:(NZW) SPF | 0.5 g in 0.4 ml dist. $H_2O$ applied to skin directly | Slight skin irritant. |
| Dermal Sensitivity (Guinea Pig Maximization Test) | guinea pigs Crl:(HA)BR | Sensitization: 5% in $H_2O$ or FCA/$H_2O$ id[b] Induction and Challenge: 25% in Petrolatum, dermal topical | **Extreme dermal sensitizer**: mild→intense skin reactions were noted in all animals in the test group; Some animals (12/20) in the test group showed subcutaneous hemorrhaging, necrosis, and desquamation in the test sites following challenge. |
| *Salmonella*/microsomal Ames Assay | *Salmonella typhimurium*: histidine auxotrophs TA97a, TA98, TA100, TA102, and TA1535 | 10-5000 μg/plate | **Mutagenic**: ≥50 μg/plate, -S9 - TA97a and TA102 ≥100 μg/plate, + S9 - TA97a 5000 μg/plate, +/- S9 - TA98 and TA100 |

## 3. ADME

### 3.1. ABSORPTION (BIOAVAILABILITY) AND TOXICOKINETICS



#### 3.1.1.Single IV Studies

Assessment of the intravenous (iv) pharmacokinetics of celecoxib was conducted in five species. The following table presents the summary of mean plasma PK parameters (SEM) following single dose iv administration of SC-58635.

| Species | Dose (mg/kg) | $t_{1/2}$ (hr) | | $Vd_{area}$ (l/kg) | | $Vd_{ss}$ (l/kg) | | Cl (ml/min/kg) | | $AUC_{0-\infty}$ (μg•hr/ml) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Rat (N=3) | 1 | 3.73 | 14.0 | 2.51 | 2.42 | ND | ND | 7.76 | 1.99 | 2.15 | 8.38 |
| Rat (N=3) | 10 | 3.49 | | 1.86 | | ND | ND | 5.81 | | 28.7 | |
| Guinea Pig (N=2) | 6 | 1.16 | | 1.98 | | ND | ND | 20.5 | | 5.49 | |
| Dog (N=3) | 1 | 3.92 (1.41) | 4.09 (1.92) | 2.30 (0.32) | 2.30 (0.59) | ND | ND | 10.0 (2.9) | 7.98 (2.00) | 2.00 (0.49) | 2.52 (.52) |
| Dog (N=2) | 5 | 8.84 | | 2.42 | | ND | ND | 3.08 | | 31.2 | |
| Dog (Fast) (N=3) | 5 | 1.77 (0.25) | 1.66 (0.16) | 2.63 (0.43) | 2.32 (0.15) | 2.18 (0.20) | 1.98 (0.05) | 19.2 (2.2) | 16.9 (1.6) | 4.95 (0.47) | 5.20 (0.47) |
| Dog (Slow) (N=3) | 5 | 4.69 (0.44) | 5.54 (0.36) | 2.95 (0.21) | 3.27 (0.21) | 2.26 (0.09) | 2.45 (0.09) | 7.43 (0.44) | 6.95 (0.45) | 11.5 (0.7) | 12.5 (0.7) |
| Cynomolgus Monkey (N=3) | 1 | | 1.66 (0.50) | | 3.58 (1.02) | | 3.22 (0.88) | | 22.7 (1.0) | | 0.736 (0.032) |
| Rhesus Monkey (N=3) | 1 | | 1.50 0.10) | | 2.73 (0.34) | | 2.34 (0.41) | | 17.8 (1.9) | | 0.957 (0.096) |

ND = Not determined.
Fast = Dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate
Slow = Dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

### 3.1.2.Single Oral Studies

A summary of mean (SEM) plasma PK parameters for SC-58635 following single dose oral administration is shown in the following table.

| Species (N) | Dose (mg/kg) | Sex | $T_{max}$ (hr) | $C_{max}$ ($\mu$g/ml) | $AUC_{0-\infty}$ ($\mu$g•hr/ml) | BA % |
|---|---|---|---|---|---|---|
| Rat (3) | 2 | ♂ | 3.00 | 0.599 | ND | ND |
| Rat (3) | 10 | ♂ | 3.00 | 2.01 | 18.5 | 64.5 |
| Dog (3) | 1 | ♂ | 1.00 (0.50) | 0.309 (0.015) | 1.57 (0.32) | 74.4 (5.6) |
| Dog (3) | 1 | ♀ | 0.667 (0.167) | 0.553 (0.070) | 2.12 (0.47) | 85.9 (20.7) |
| Dog (2) | 5 | ♀ | 0.500 | 2.19 | 16.2 | 57.1 |
| Dog (2) | 5 | ♀ | 3.00 | 0.517 | 4.80 | 16.9 |
| Dog-Fast (3) | 5 | ♂ & ♀ | 0.667 (0.167) | 0.822 (0.219) | 2.63 (0.59) | 63.7 (10.5) |
| Dog-Slow (3) | 5 | ♂ & ♀ | 0.500 (0) | 1.54 (0.19) | 10.5 (1.6) | 88.0 (5.8) |

ND = Not determined; N = The number of animals.
Fast = Dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate.
Slow = Dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.



The following table presents the food effect on mean SC-58635 PK (±SEM) parameters in beagle dogs.

| Site of Absorption and Food Effect Studies in Beagle Dogs | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg) | Route | Diet | $T_{max}$ (hr) | | $C_{max}$ ($\mu$g/ml) | | $AUC_{0-24}$ ($\mu$g•hr/ml) | |
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 10 n=4 | IG[a] | Fasted | | 0.688 ± 0.277 | | 1.62 ± 0.36 | | 10.3 ± 2.0 |
| | Duodenum[a] | | | 1.13 ± 0.63 | | 1.46 ± 0.20 | | 9.69 ± 1.57 |
| | Jejunum[a] | | | 2.25 ± 1.92 | | 1.06 ± 0.21 | | 9.37 ± 0.97 |
| | Colon[a] | | | 8.50 ± 2.02 | | 0.789 ± 0.118 | | 10.0 ± 0.9 |
| 5 n=3/sex | IG[b] | Fasted | 1.50 ± 0.29 | 7.50 ± 5.27 | 0.356 ± 0.163 | 0.364 ± 0.035 | 1.89 ± 1.01 | 3.32 ± 0.28 |
| | | Low Fat | 3.00 ± 0.50 | 3.67 ± 1.17 | 0.712 ± 0.227 | 0.775 ± 0.064 | 5.63 ± 1.94 | 5.58 ± 1.09 |
| | | Med. Fat | 5.33 ± 0.67 | 4.67 ± 0.67 | 0.706 ± 0.148 | 0.631 ± 0.080 | 5.07 ± 1.35 | 5.07 ± 0.83 |
| | | High Fat | 6.00 ± 1.15 | 5.33 ± 1.76 | 0.737 ± 0.115 | 0.808 ± 1.06 | 6.64 ± 1.73 | 6.66 ± 1.34 |

[a]SC-58635 was administered as a solution in PEG:$H_2O$, 2:1, (v/v) or in PEG:Saline, 2:1, (v/v).
[b]SC-58635 was administered as neat chemical in a gelatin capsule.
Med. Fat = Medium Fat ; IG = Intragastrically.

## 3.1.3.Repeated-Dose Oral Toxicity Studies

### Mouse Studies

The following table summarizes PK parameters obtained from 2-, 13-, and 104-week oral toxicity studies.

**2-Week Diet Admix Study in Mice, EX4325**

| Dose (mg/kg) | $C_{max}$ (μg/ml) ♂ | $C_{max}$ (μg/ml) ♀ | $AUC_{0-21}$ (μg•hr/ml) ♂ | $AUC_{0-21}$ (μg•hr/ml) ♀ |
|---|---|---|---|---|
| 100 | 3.52 | 1.52 | 55.8 | 20.4 |
| 300 | 10.4 | 4.54 | 148 | 60.5 |
| 1000 | 19.7 | 10.6 | 288 | 162 |

**13-Week Diet Admix Range-Finding Study in Mice, EX4357**

| Dose (mg/kg) ♂ | Dose (mg/kg) ♀ | $C_{max}$ (μg/ml) ♂ Day 1 | ♂ Day 45 | ♂ Day 87 | $C_{max}$ (μg/ml) ♀ Day 1 | ♀ Day 45 | ♀ Day 87 | $AUC_{0-\infty}$ (μg•hr/ml) ♂ Day 1 | ♂ Day 45 | ♂ Day 87 | $AUC_{0-\infty}$ (μg•hr/ml) ♀ Day 1 | ♀ Day 45 | ♀ Day 87 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 75 | 150 | 2.78 | 2.00 | 2.44 | 2.99 | 1.92 | 2.04 | 38.7 | 32.2 | 39.6 | 42.1 | 24.2 | 30.8 |
| 150 | 300 | 6.71 | 4.62 | 3.79 | 6.22 | 2.79 | 3.55 | 84.7 | 70.7 | 57.2 | 85.3 | 47.0 | 48.0 |
| 300 | 1000 | 12.8 | 8.27 | 6.65 | 14.6 | 12.8 | 11.5 | 216 | 153 | 123 | 226 | 181 | 183 |

**104-Week Diet Admix Carcinogenicity Study, SA4452**

| Week (Days) | Dose (mg/kg) ♂ Wk1-18 | ♂ Wk 19-104 | ♀ Wk1-18 | ♀ Wk19-22 | ♀ Wk 23-80 | $C_{max}$ (μg/ml) ♂ | $C_{max}$ (μg/ml) ♀ | $AUC_{0-24}$ (μg•hr/ml) ♂ | $AUC_{0-24}$ (μg•hr/ml) ♀ |
|---|---|---|---|---|---|---|---|---|---|
| 1 (3-4) | 25 | 12.5 | 50 | 25 | 25 | 0.973 | 0.807 | 11.1 | 12.3 |
| | 50 | 25 | 100 | 50 | 50 | 1.73 | 2.73 | 22.0 | 29.9 |
| | 75 | 37.5 | 150 | 75 | 150 | 2.55 | 2.65 | 34.7 | 33.8 |
| 19 (126-127) | 25 | 12.5 | 50 | 25 | 25 | 0. 865 | 0.555 | 13.5 | 7.05 |
| | 50 | 25 | 100 | 50 | 50 | 1.75 | 0. 815 | 32.8 | 14.3 |
| | 75 | 37.5 | 150 | 75 | 150 | 2.69 | 0.699 | 50.8 | 13.8 |
| 52 (357-358) | 25 | 12.5 | 50 | 25 | 25 | 0.328 | 0. 290 | 6.43 | 4.31 |
| | 50 | 25 | 100 | 50 | 50 | 0.723 | 0.558 | 13.2 | 8.14 |
| | 75 | 37.5 | 150 | 75 | 150 | 1.24 | 0.967 | 22.8 | 17.6 |
| 78 (540-541) | 25 | 12.5 | 50 | 25 | 25 | 0.479 | 0.335 | 9.22 | 5.99 |
| | 50 | 25 | 100 | 50 | 50 | 0.933 | 0.813 | 16.4 | 12.9 |
| | 75 | 37.5 | 150 | 75 | 150 | 1. 22 | 1.84 | 25.0 | 26.5 |

Rat Studies

The following table summarizes PK parameters obtained from 4-, 13-, 26-, and 104-week oral toxicity studies.

**4-Week Oral Toxicity Study (SA4261)**

| Dose (mg/kg) | $C_{max}$ (μg/ml) | | | | $AUC_{0-24}$ (μg•hr/ml) | | | |
|---|---|---|---|---|---|---|---|---|
| | Day 1 | | Day 26 | | Day 1 | | Day 26 | |
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 20 | 2.60 | 3.44 | 1.57 | 2.63 | 30.3 | 41.8 | 19.2 | 36.0 |
| 80 | 5.19 | 7.64 | 3.09 | 5.55 | 73.2 | 118 | 29.7 | 82.0 |
| 400 | 10.3 | 12.3 | 5.85 | 9.60 | 196 | 245 | 60.7 | 159 |
| 600 | 6.71 | 13.9 | 5.53 | 16.2 | 97.6 | 276 | 58.2 | 315 |

**13- and 26-Week Oral Toxicity Studies (SA4346 and SA4366*)**

| Dose | $C_{max}$ (μg/ml) | | | | | | | | $AUC_{0-24}$ (μg•hr/ml) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (mg/kg) | Day 1 | | Day 42 | | Day 91 | | Day 182* | | Day 1 | | Day 42 | | Day 91 | | Day 182* | |
| 20 | 2.47 | 2.91 | 1.68 | 3.06 | 1.75 | 2.20 | 2.03 | 4.05 | 22.0 | 38.3 | 17.6 | 36.9 | 18.9 | 34.2 | 26.5 | 52.5 |
| 80 | 3.79 | 5.99 | 2.58 | 6.86 | 2.49 | 4.26 | 2.97 | 6.94 | 42.4 | 83.5 | 23.4 | 90.3 | 36.3 | 75.4 | 41.5 | 101 |
| 400 | 6.50 | 11.6 | 4.36 | 6.80 | 3.91 | 7.19 | 5.12 | 10.5 | 78.8 | 149 | 66.1 | 100 | 58.3 | 105 | 54.6 | 150 |

**104-Week Carcinogenicity Study (SA4367)**

| Group | Dose mg/kg/day | PK Parameter | Day 1 (Wk1) | | Day 180 (Wk 26) | | Day 359 (Wk 52) | | Day 541 (Wk 78) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Low | 20<br>5 | $C_{max}$ (μg/ml) | 1.93 | 2.65 | 2.16 | 3.41 | 2.00 | 4.75 | 1.45 | 1.11 |
| Mid | 80<br>10 | | 3.42 | 5.63 | 3.09 | 7.46 | 2.88 | 7.44 | 0.893 | 2.00 |
| High | 400<br>200 | | 6.09 | 10.1 | 4.62 | 7.93 | 4.71 | 9.47 | 4.28 | 13.0 |
| Low | 20<br>5 | $AUC_{0-24}$ (μg•hr/ml) | 18.7 | 39.1 | 22.6 | 51.6 | 24.8 | 72.8 | 20.8 | 17.9 |
| Mid | 80<br>10 | | 42.6 | 81.2 | 39.0 | 111 | 38.2 | 114 | 11.6 | 27.7 |
| High | 400<br>200 | | 95.1 | 163 | 56.8 | 118 | 73.4 | 158 | 66.7 | 132 |

The following table summarizes PK parameters obtained from reproductive toxicity studies.

| Pre-Mating and Early Pregnancy Study in Rats | | | | |
|---|---|---|---|---|
| Dose | $C_{max}$ (μg/ml) | | $AUC_{0-24}$ (μg•hr/ml) | |
| (mg/kg) | Day 1[a] | Day 23[b] | Day 1 | Day 23 |
| 5 | 1.84 | 1.63 | 25.6 | 23.3 |
| 15 | 3.59 | 3.35 | 57.6 | 47.2 |
| 30 | 3.96 | 5.17 | 70.6 | 63.3 |
| 50 | 5.93 | 5.25 | 95.7 | 90.9 |
| [a] Animals were dosed 14 days prior to mating, throughout the mating period until day 7 of gestation. The total dosing period was approximately 23 days. [b] Gestation Day 7 | | | | |
| **Embryo-Fetal Development Toxicity Studies in Rat (n=6/dose)** | | | | |
| Dose | $C_{max}$ (μg/ml) | | $AUC_{0-24}$ (μg•hr/ml) | |
| (mg/kg) | Gestation Day 6 | Gestation Day 16/17 | Gestation Day 6 | Gestation Day 16/17 |
| SA4362 - Animals were dosed once daily from day 6 to day 16 of gestation. | | | | |
| 10 | 1.79 | 2.81 | 20.3 | 37.1 |
| 30 | 3.01 | 5.03 | 43.9 | 67.0 |
| 100 | 6.37 | 7.45 | 134 | 115 |
| SA4599 - Animals were dosed once daily from day 6 to day 17 of gestation. | | | | |
| 10 | 3.79 | 3.20 | 45.7 | 47.6 |
| 30 | 4.91 | 5.43 | 54.3 | 104 |
| 100 | 7.66 | 7.41 | 140 | 115 |
| **Embryo-Fetal Development Toxicity Studies in Rabbit, SA4342 (n=6/dose)** | | | | |
| | Gestation Day 7 | Gestation Day 19 | Gestation Day 7 | Gestation Day 19 |
| 60 | 0.951 | 1.49 | 14.9 | 22.5 |
| 150 | 1.41 | 2.37 | 24.5 | 41.5 |
| 300 | 1.76 | 5.14 | 37.4 | 89.0 |



## Dog Studies

Mean PK (±SEM) parameters for SC-58635 obtained from 4-, 13-, 26/52-week oral toxicity studies are summarized in the following tables.

| 4-Week Oral Safety Assessment Study in the Dog, SA4260 | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day of Dosing | Dose (mg/kg)[a] | $C_{max}$ (μg/ml) | | | $AUC_{0-24}$ (μg•hr/ml) | | |
| | | ♂ | ♀ | ♂+♀ | ♂ | ♀ | ♂+♀ |
| 1 | 25 (n=4) | 1.90 ± 0.79 | 1.72 ± 0.42 | 1.81 ± 0.42 | 21.7 ± 10.9 | 18.7 ± 6.7 | 20.2 ± 6.0 |
| | 50 (n=4) | 4.15 ± 1.42 | 1.94 ± 0.66 | 3.04 ± 0.84 | 47.7 ± 13.3 | 25.4 ± 10.4 | 36.6 ± 8.9 |
| | 100 (n=8) | 6.89 ± 1.54 | 3.96 ± 0.89 | 5.42 ± 0.94 | 104 ± 30 | 71.0 ± 19.9 | 87.3 ± 17.9 |
| | 250 (n=8) | 10.3 ± 3.1 | 8.44 ± 2.05 | 9.37 ± 1.82 | 153 ± 53 | 120 ± 36 | 136 ± 31 |
| 15 | 100 | 8.35 ± 2.71 | 8.72 ± 3.34 | 8.51 ± 2.02 | 117 ± 41 | 104 ± 36 | 111 ± 27 |
| | 250 | 7.72 ± 2.98 | 12.0 ± 3.9 | 9.85 ± 2.43 | 135 ± 67 | 211 ± 80 | 173 ± 51 |
| 27 | 25 | 4.62 ± 2.58 | 2.27 ± 0.65 | 3.45 ± 1.31 | 71.5 ± 50.9 | 22.2 ± 7.8 | 46.9 ± 25.6 |
| | 50 | 6.77 ± 2.10 | 4.66 ± 2.04 | 5.86 ± 1.43 | 83.7 ± 30.2 | 60.6 ± 30.0 | 73.8 ± 20.3 |

[a] The 100 and 250 mg/kg dose groups were sacrificed on day 15 of dosing. The 25 and 50 mg/kg dose groups were sacrificed on day 27 of dosing. Reference: Document Number MRC-94S-0185.

| 13-Week Oral Safety Assessment Study in the Dog (SA4324) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose (mg/kg) | Phenotype[b] | $C_{max}$ (μg/ml)[a] | | | $AUC_{0-24}$ (μg•hr/ml) | | |
| | | Day 1 | Day 39 | Day 88 | Day 1 | Day 39 | Day 88 |
| 7.5 (bid) | Fast | 1.04 ± 0.11 | 1.03 ± 0.11 | 0.802 ± 0.251 | 6.88 ± 1.33 | 5.79 ± 1.13 | 7.11 ± 2.70 |
| | Slow | 2.19 ± 0.36 | 1.75 ± 0.23 | 2.19 ± 0.32 | 17.3 ± 2.9 | 19.3 ± 2.5 | 21.0 ± 3.0 |
| 12.5 (bid) | Fast | 1.75 ± 0.32 | 1.55 ± 0.14 | 1.33 ± 0.15 | 10.1 ± 1.0 | 12.6 ± 0.6 | 11.0 ± 1.7 |
| | Slow | 1.81 ± 0.49 | 2.39 ± 0.15 | 2.13 ± 0.35 | 15.2 ± 4.6 | 24.8 5.0 | 22.9 ± 5.5 |
| 17.5 (bid) | Fast | 1.53 ± 0.26 | 2.16 ± 0.41 | 2.12 ± 0.41 | 12.8 ± 2.2 | 17.3 ± 3.4 | 17.0 ± 3.9 |
| | Slow | 2.76 ± 0.43 | 3.74 ± 0.40 | 3.14 ± 0.43 | 25.8 ± 3.5 | 43.0 ± 4.7 | 38.0 ± 4.4 |
| 25 (qd) | Fast | 0.800 ± 0.329 | 0.326 ± 0.119 | 0.490 ± 0.046 | 6.18 ± 2.54 | 2.77 ± 1.52 | 3.18 ± 0.74 |
| | Slow | 0.916 ± 0.215 | 0.846 ± 0.182 | 0.860 ± 0.316 | 7.27 ± 1.52 | 9.41 ± 3.67 | 10.9 ± 5.1 |
| **26/52-Week Oral Safety Assessment Study in the Dog (SA4324)** | | | | | | | |
| Dose (mg/kg) | Phenotype | $C_{max}$ (μg/ml)[b] | | | $AUC_{0-24}$ (μg•hr/ml) | | |
| | | Day 1 | Day 178 | Day 360 | Day 1 | Day 178 | Day 360 |
| 7.5 (bid) | Fast | 0.917 ± 0.238 | 0.832± 0.091 | 0.725 ± 0.083 | 5.16 ± 0.96 | 5.89 ± 0.63 | 5.61 ± 1.39 |
| | Slow | 2.01 ± 0.36 | 1.91 ± 0.38 | 1.91 ± 0.12 | 18.2 ± 2.1 | 21.2 ± 4.6 | 22.8 ± 4.7 |
| 12.5 (bid) | Fast | 1.14 ± 0.28 | 2.15 ± 0.32 | 1.79 ± 0.36 | 9.22 ± 2.29 | 15.6 ± 3.9 | 15.1 ± 5.2 |
| | Slow | 2.04 ± 0.30 | 2.86 ± 0.39 | 2.53 ± 0.36 | 20.1 ± 3.4 | 30.9 ± 3.2 | 33.4 ± 6.5 |
| 17.5 (bid) | Fast | 1.07 ± 0.13 | 1.76 ± 0.23 | 1.47 ± 0.20 | 8.92 ± 1.42 | 11.4 ± 1.3 | 11.8 ± 1.7 |
| | Slow | 2.61 ± 0.40 | 3.61 ± 0.19 | 3.11 ± 0.29 | 28.7 ± 5.3 | 40.6 ± 3.1 | 37.2 ± 5.0 |
| 25 (qd) | Fast | 0.774 ± 0.254 | 0.537 ± 0.160 | 0.651 ± 0.235 | 4.00 ± 2.02 | 2.98 ± 0.88 | 3.86 ± 2.02 |
| | Slow | 1.94 ± 0.56 | 0.951 ± 0.186 | 0.886 ± 0.153 | 23.7 ± 7.4 | 10.6 ± 3.9 | 7.38 ± 1.28 |

[a] The $C_{max}$ value reported is the maximal plasma SC-58635 concentration obtained over a 24 hour dosing day.

[b] Phenotype: Fast are dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate. Slow are dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

The following table shows the comparison of exposures to SC-58635 on last day of dosing in rat and dog toxicity studies to clinical human exposures at 200 and 400 mg/day.

| Species | Duration | Sex/ Pheno-type[b] | NOEL (mg/kg) | Animal Exposure (Last Day of Dosing) | | Animal/Human Exposure Ratio[a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $C_{max}$ (μg/ml) | $AUC_{0-24}$ (μg•hr/ml) | 200 mg/day | | 400 mg/day | |
| | | | | | | $C_{max}$ | $AUC_{0-24}$ | $C_{max}$ | $AUC_{0-24}$ |
| Rat | 4-Wk | ♂ | 80 | | | | | | |
| | | ♀ | 400 | 9.60 | 159 | 14.2 | 18.9 | 7.1 | 9.5 |
| Rat | 13-Wk | ♂ | 20 | 1.75 | 18.9 | 2.6 | 2.3 | 1.3 | 1.1 |
| | | ♀ | 20 | 2.20 | 34.2 | 3.3 | 4.1 | 1.6 | 2.0 |
| Rat | 6-Mon | ♂ | 20 | 2.03 | 26.5 | 3.0 | 3.2 | 1.5 | 1.6 |
| | | ♀ | 20 | 4.05 | 52.5 | 6.0 | 6.3 | 3.0 | 3.1 |
| Dog | 4-Wk | ♂ | 25 | 2.27 | 22.2 | 3.4 | 2.6 | 1.7 | 1.3 |
| | | ♀ | 25 | 4.62 | 71.5 | 6.8 | 8.5 | 3.4 | 4.3 |
| Dog | 13-Wk | Fast (♂ & ♀) | 35 | 2.12 | 17.0 | 3.1 | 2.0 | 1.6 | 1.0 |
| | | Slow (♂ & ♀) | 35 | 3.14 | 38.0 | 4.7 | 4.5 | 2.3 | 2.3 |
| Dog | 6-Mon | Fast (♂ & ♀) | 35 | 1.76 | 11.4 | 2.6 | 1.4 | 1.3 | 0.7 |
| | | Slow (♂ & ♀) | 35 | 3.61 | 40.6 | 5.3 | 4.8 | 2.7 | 2.4 |
| Dog | 1-Year | Fast (♂ & ♀) | 35 | 1.47 | 11.8 | 2.2 | 1.4 | 1.1 | 0.7 |
| | | Slow (♂ & ♀) | 35 | 3.11 | 37.2 | 4.6 | 4.4 | 2.3 | 2.2 |



[a] The mean $C_{max}$ and $AUC_{0-24}$ values for the 200 mg/day dose were 0.675 μg/ml and 8.40 μg•hr/ml, respectively. The mean $C_{max}$ and $AUC_{0-24hr}$ values for the 400 mg/day dose were 1.35 μg/ml and 16.8 μg•hr/ml, respectively. Ratio was calculated by dividing animal Day last $AUC_{0-24}$ or $C_{max}$ values by respective human values.

[b] Phenotype: Fast are dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate. Slow are dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

### *3.2. TISSUE DISTRIBUTION*

Celecoxib was well distributed into the majority of tissues as demonstrated by a rat tissue distribution study. Following an oral dose of 2 mg/kg celecoxib, the gastrointestinal tract tissues contained the highest concentrations of radioactivity, with high levels of radioactivity also

found in liver, red blood cells, adrenal glands, lacrimal glands and bone marrow. The concentrations of radioactivity in skin were the same as that of plasma, indicating that there was no preferential partitioning of celecoxib and/or its metabolites into skin. The concentrations of radioactivity in pigmented and nonpigmented skin were similar and decreased at similar rates, indicating no irreversible or extensive binding of celecoxib to melanin. By 96 hours post dose, concentrations of radioactivity in most tissues were below the limit of detection.

Data from the whole-body autoradiography study (iv bolus loading dose of celecoxib at 2 mg/kg followed by a 5-hour IV infusion dose of celecoxib at 0.4 mg/kg/hr) showed that highly perfused tissues, namely liver, heart, lungs, and kidney, and intestinal contents contained the largest amounts of radioactivity. Smaller levels of radioactivity were observed in the stomach, lining of the cecum and intestines, harderian gland, adrenal gland, pancreas, bone marrow, blood, brain, spinal cord, testes, skin and hair follicles.

### *3.3. METABOLISM*

Celecoxib was metabolized by a single metabolic pathway in all species studied (mouse, rat, dog, rabbit, and monkey). Hydroxylation of the aromatic methyl group of celecoxib to form SC-60613 was the initial step in the metabolism of SC-58635. Then, the hydroxyl group of SC-60613 was further oxidized to a carboxyl to form SC-62807. SC-60613 and SC-62807 were metabolites produced by rat, dog, cynomolgus monkey and rhesus monkey. The glucuronide conjugates of SC-60613 and SC-62807 were present in bile of rat. The glucuronide conjugate of SC-62807 and the dual glucuronide glycine conjugate of SC-62807 were present in rabbit urine. SC-60613 and SC-62807 have been synthesized and shown not to have any inhibitory activity to COX-1 or COX-2. The metabolism of celecoxib by the animal species studied was similar to that for human, i.e. hydroxylation of celecoxib to SC-60613 and further oxidation to the carboxylic acid, SC-62807. The 1-O-glucuronide of SC-62907 is a minor metabolite in human.

*In vitro* metabolism of celecoxib was studied in the rat, dog, and human. Data showed that (1) celecoxib was a mild inducer of CYP2B but not CYP3A in the rat; (2) CYP2D15 was important for the metabolism of celecoxib in the dog; and (3) CYP2C9 and CYP3A4 were the most important cytochrome enzymes involved in the metabolism of celecoxib in the human.

### *3.4. PLASMA PROTEIN BINDING*

The plasma protein binding of SC-58635 was evaluated *in vivo*. Approximately 95% of celecoxib bound to plasma protein following oral administration to the mouse, rat and dog. Similar data were noted in the *in vitro* studies. The following table summarizes results expressed as % binding of [$^{14}$C]SC-58635 obtained from *in vitro* protein binding studies.

| [$^{14}$C]SC-58635 (μg/ml) | Method | Mouse Plasma | Rat Plasma | Dog Plasma | Human Plasma | Human Albumin (40 mg/ml)[a] | Human AAG (1.8 mg/ml)[a] |
|---|---|---|---|---|---|---|---|
| 0.1 | | 94.4 | 98.4 | 98.2 | 98.2 | 100 | 92.4 |
| 0.3 | | ND | 94.3 | 96.7 | 97.9 | 100 | 91.6 |
| 1 | | ND | 91.4 | 97.0 | 96.5 | 99.8 | 91.0 |
| 3 | | ND | 95.9 | 97.0 | 96.7 | 99.9 | 88.4 |
| 10 | | 93.5 | 84.2 | 97.1 | 96.3 | 99.8 | 78.6 |
| 0.3 | | ND | 95.6 | ND | 97.3 | ND | ND |
| 1 | | ND | 85.3 | ND | ND | ND | ND |
| 3 | | ND | 88.3 | ND | 90.6 | ND | ND |

ND - Not Determined.

AAG = $\alpha_1$ acid glycoprotein.

[a] These concentrations reflect values in normal human.

*3.5. EXCRETIONS*

Studies in the rat, dog, cynomolgus monkey, and Rhesus monkey showed that biliary/intestinal excretion was the major route for the elimination of celecoxib following a single iv dose with values of 90%, 90%, 65%, and 80%, respectively. The remaining dose was eliminated through urine. SC-62807, the carboxylic acid metabolite, was the major metabolite excreted in both urine and feces. Celecoxib was metabolized extensively in all species studied by the evidence of little or no unchanged drug excreted in urine or bile.

*3.6. PLACENTAL TRANSFER AND MILK SECRETION*

Secretion of celecoxib through milk was evaluated in the lactating SD rats by given a single oral dose of 5 mg SC-58635 via gavage. The concentrations of celecoxib in maternal plasma and milk were similar, indicating that celecoxib was distributed to milk and available to the neonate. In addition, celecoxib was present in plasma of neonates from dams that were administered the test article.

Placental transfer of celecoxib was studied by giving a single oral dose mg/kg celecoxib to pregnant rats (n=18) at approximately day 18 of gestation. Results showed that the concentrations of celecoxib in maternal plasma and fetuses were similar, indicating that celecoxib crossed the placenta and was available to the fetus.

## CONCLUSION:

It appeared that GI and kidney were major target organs for SC-58635 induced toxicity following repeated oral administration to the mouse and rat.

GI injury with low incidence of interdigital pyoderma/subcutis abscess were observed in dogs treated with doses ≥50 mg/kg/day (equivalent to of human exposure at 400 mg/day dose as measured by $AUC_{0-24}$) for 4-week. **Similar findings of cutaneous lesions were observed in dogs treated with other COX-2 inhibitors. Although these observations occurred at low incidence and did not appear to be dose-dependent, test-article caused toxicity through the mechanism by inhibiting phagocytic cell functions could not be ruled out. Therefore, close monitoring of adverse events of microbial infections in addition to GI injury in humans is highly recommended.** Additionally, there were lesions with slight→mild chronic multifocal perivascular/periventricular lymphocytic infiltrate identified in a dog 4-week toxicity study. These pathological changes within brain are often seen in dogs with viral infection with CNS involvement. Information from a rat study implied that SC-58635 could pass blood-brain-barrier (BBB) and rapidly distribute into CNS tissues as the levels of SC-58635 in CNS were higher than blood following an oral administration of 10 mg/kg. Therefore, the observations of theses changes may be attributable to drug-caused toxicity. It would be beneficial to conduct additional studies to distinguish whether such lesions are drug-induced or due to underlying viral inflammatory diseases of the CNS or other causes.

The effects of SC-58635 on pancreatic functions were not investigated in the current submission. It has been shown that COX-2 constitutively expressed in the pancreatic tissue (HIT-T15 cells, Syrian hamster islets and human pancreatic islets) under basal and stimulated condition[5]. Thus, the pharmacological or undesirable toxicological effects of SC-58635 on β-cells and blood glucose levels following long term use need to be addressed.

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5 Sorli CH, et al., 1998. Proc. Natl. Acad. Sci. USA 95: 1788-1793.

## DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS

## PHARMACOLOGY AND TOXICOLOGY REVIEW

**NDA** 20-998

**DRUG:** Celecoxib; Celebrex™; SC-58635

**SPONSOR:** G.D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

**DRAFT**

**SUBMISSION DATE:** June 29, 1998

**TYPE OF SUBMISSION:** Original [505 (b)(1)]

**DATE COMPLETED:** November 3, 1998

**REVIEWER:** W. C. Josie Yang, Ph.D.

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**CDER STAMP DATE:** July 1, 1998

**DATE RECEIVED IN HFD-550:** July 3, 1998

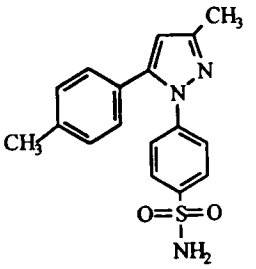
**DATE ASSIGNED TO REVIEWER:** July 14, 1998

**USER FEE DUE DATE:** **December 31, 1998**

**DRUG CATEGORY:** Nonsteroidal Anti-inflammatory & Analgesic [Inhibitor of Cyclooxygenase 2 (COX-2)]

**FORMULA:** 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide ($C_{17}H_{14}F_3N_3O_2S$); M.W.: 381.38

| INGREDIENTS | QUANTITIES (MG) | | FUNCTION |
|---|---|---|---|
| | 100 mg Capsule | 200 mg Capsule | |
| Celecoxib | | | Active Ingredient |
| Lactose | | | |
| Na Laury Sulfate | | | |
| Povidone | | | |
| Croscarmellose Na | | | |
| Mg Stearate | | | |



SC-58635

**CAS Nº:** 169590-42-5

**INDICATION:** For acute and chronic treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis; and for the management of acute and chronic pain.

**DOSAGE FORM:** Capsules, 100 and 200 mg

**RELATED DRUG/INDs/NDAs/DMFs:**

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NDA 20-998 Celecoxib (Celebrex™)

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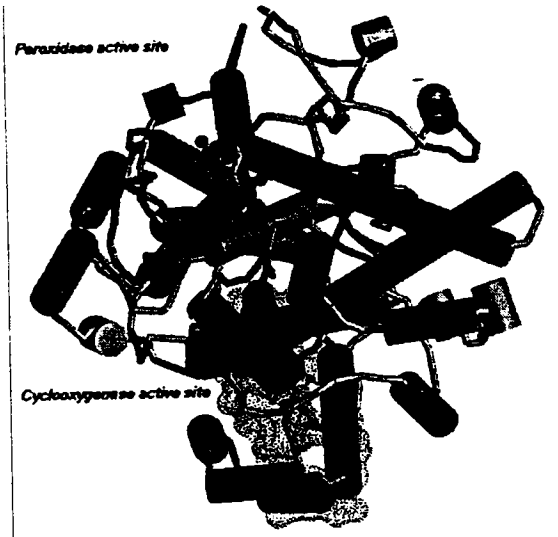
# 1. PHARMACOLOGY

## 1.1. OVERVIEW




The actions of currently available NSAIDs in the market to inhibit the production of prostaglandins (PGs) by cyclooxygenases (COX) can be divided into three categories: (i) modification of the enzymes by acetylation of a serine residue at the active site, such as aspirin; (ii) induction of time-dependent irreversible inhibition of enzymes, such as indomethacin or flurbiprofen; (iii) induction of reversible competitive inhibition, such as ibuprofen and mefenamate. Two distinct COX enzymes were identified recently. COX-1, a constitutively expressed form, displays in gut and kidney that produce PGs which are required for normal physiological functions. COX-2, an inducible isoenzyme, is encoded by a different gene from COX-1 and only exists in high concentrations under the inflammatory condition or following mitogenic stimulation. COX-1 mRNA could be detected in all tissues with highest expressed levels found in platelets, vascular endothelial cells, liver, stomach, spleen, kidney collecting tubules and colon. In contrast, COX-2 mRNA levels were extremely low in all normal tissues except rat brain. Both enzymes have approximately 60% homology and are able to convert arachidonic acid to $PGH_2$ with similar affinity. The amino acid residues thought to be essential for this enzymatic conversion are conserved in both structures.

GI toxicity, a common side effect of NSAIDs, is believed to be caused by the inhibition of PGs which were regulated by COX-1 in the GI tract and required for normal physiological function. The present submission introduced celecoxib (SC-58635 - $C_{17}H_{14}F_3N_3O_2S$), a newly developed COX-2 inhibitor, which is a diarylsubstituted pyrazole compound. The physical interactions between celecoxib and COX-2 are illustrated in the above figure (1.5 13). Celecoxib is proposed for the treatment of the signs and symptoms of RA and OA, and for the management of acute and chronic pain.

## 1.2. GENERAL AND MECHANISM-RELATED PHARMACOLOGY

### *1.2.1. IN VITRO SELECTIVITY FOR COX-2 (REF. 1-3, 5, 6, 11, 13)*

- Inhibition of $PGE_2$, $TXB_2$, or LTB4 Production by Human Fetal Skin Fibroblasts or Whole blood -

| | SC-58635 $IC_{50}$ ($\mu$M) | | | |
|---|---|---|---|---|
| Cell Type | Human Fetal Skin Fibroblast | Human Whole Blood | | |
| | IL-1 Induced COX-2 Mediated $PGE_2$ Production | A23187-Induced COX-1 Mediated $TXB_2$ | 5-LO[a] Mediated LTB4 | LPS-Induced COX-2 Mediated $PGE_2$ Production |
| Expt. 1 | 0.3 ± 0.1 (n=7) | 1.6 ± 0.3 (n=6) | 2.4 ± 0.5 (n=4) | 0.139 ± 0.04 (n=4) |
| Expt. 2 | - | 6.665 ± 1.081 (n=3) | - | 0.164 ± 0.06 (n=7) |

[a] 5-LO = 5-lipoxygenase

- Inhibition of $O_2$ Consumption and Peroxidase -

| Parameters Measured | $IC_{50}$ (μM) | |
|---|---|---|
| | Sheep COX-1 | hCOX-2 |
| Oxygen Consumption | 50 | 0.2 |
| Peroxidase Activity | 10 | 0.2 |

- Inhibition of $PGE_2$ Production Mediated by Recombinant COX-1 and COX-2 -

| Treatment | $IC_{50}$ (μM) | |
|---|---|---|
| | hCOX-1 | hCOX-2 |
| Indomethacin | 0.1 ± 0.07 (n=147) | 1.10 ± 0.50 (n=148) |
| SC-58635 | 15 ± 3.40 (n=7) | 0.04 ± 0.01 (n=7) |
| SC-59046 | 36 ± 13.0 (n=9) | 0.05 ± 0.02 (n=10) |

- *Ex Vivo* Inhibition of A23187-induced COX-1 Mediated TBX2 Production by Rat Whole Blood -

| Treatment | Dose (mg/kg) | Route | Duration (day) | A23187-induced TBX2 |
|---|---|---|---|---|
| SC-58635 | 10, 30 | po | 1 | ↔ (no effect) |
| | 15 bid | po | 1 | ↔ |
| | 600 | po | 3 or 7 | ↓ |
| Indomethacin | 5 | po | 1 | ↓ 93% |
| | 4 | po | 7 | ↓ >99% |

- Inhibition of $PGE_2$, $TXB_2$, or LTB4 Production by Dog Whole blood -

| Treatment | $IC_{50}$ (μM) | |
|---|---|---|
| | AA-Induced COX-1 Mediated $TXB_2$ Production | LPS-Induced COX-2 Mediated $PGE_2$ Production |
| SC-58635 | 1.96 ± 0.59 (n=4) | 0.46 ± 0.13 (n=9) |
| SC-59046 | 2.32 ± 0.57 (n=4) | 0.20 ± 0.07 (n=3) |
| Indomethacin | 0.16 ± 0.05 (n=4) | 0.28 ± 0.08 (n=6) |

AA = arachidonic acid

### *1.2.2. In Vivo Selectivity For COX-2 (Ref. 5, 7, 10, 15)*

- In Vivo Effects on Tissue $PGE_2$ Levels

| Study | Species Nº/group | Dose/Route/Duration | Observations |
|---|---|---|---|
| Carrageenan Induced $PGE_2$ Production in | ♂ Lewis Rat 5/group | mg/kg ig | Dose-dependent ↓ of $PGE_2$ and 6-keto $PGE_{1\alpha}$ with an $ED_{50}$ of 0.2 ± 0.1 mg/kg. |
| $PGE_2$ in Carrageenan Induced Air Pouch and Stomach | ♂ Fasted Lewis Rat 6/group | mg/kg po | Dose-dependent ↓ of $PGE_2$ in subcutaneous air pouch with an $ED_{50}$ of 0.97 ± 0.1 mg/kg.<br>Non-dose dependent ↓ of stomach $PGE_2$ production by at all doses. |
| $PGE_2$ in Various Tissues | ♂ Rat, 6/group | 600 mg/kg/day po x7 | ↓ $PGE_2$ in kidney (65.6%), stomach (48%), stomach mucosa (59.1%), duodenum (38.5%), caecum (58.5%), and colon (32.3%). |
| | ♀ Rat, 8/group | 600 mg/kg/day po x3 or x7 | ↓ $PGE_2$ in stomach (53%), stomach mucosa duodenum (28.8%), and colon |
| $PGE_2$ in CFS | ♂ Lewis Rat Adjuvant Arthritis | 0.3, 3, or 10 mg/kg po | 0.3 mg/kg - ↓ $PGE_2$ by 94% at 4 hr and 75% at 8 hr post dose.<br>≥3 mg/kg - completely ↓ $PGE_2$. |
| $PGE_2$ Paw Exudate/Synovial Fluid | | | 0.3 mg/kg - ↔ on $PGE_2$ in paw exudate.<br>3 mg/kg - ↓ $PGE_2$ by 49% at 4 hr and 34% at 8 hr post dose.<br>10 mg/kg - ↓ $PGE_2$ by 61% at 4 hr and 81% at 8 hr post dose. |

## 1.3. *In Vivo* Effects Related to Proposed Therapeutic Indications

### *1.3.1. Anti-Inflammatory Effects (Ref. 7, 8, 14)*

| Models | Species | Dose(mg/kg)/Route | Observations |
|---|---|---|---|
| Carrageenan Induced Paw Edema | ♂ SD rats | mg/kg ig | Dose-dependent ↓ paw edema with an $ED_{50}$ of 7 ± 1 mg/kg. |
| Adjuvant Arthritis | ♂ Lewis Rat | mg/kg bid ig x10 | Dose-dependent ↓ paw edema with an $ED_{50}$ of 0.3 ± 0.1mg/kg. |
| Carrageenan Induced $PGE_2$ Production in Air Pouch | ♂ Lewis Rat | ) mg/kg ig | Dose-dependent ↓ of $PGE_2$ and 6-keto $PGE_{1\alpha}$ with an $ED_{50}$ of 0.2 ± 0.1mg/kg. |
| Adjuvant Arthritis | Lewis Rat | 1 mg/kg po x10 | ↓ synovial inflammation (21%), cartilage destruction (76%), bone lysis (60%), bone proliferation (40%), and edema of soft tissue (72%). |

ig = intragastrical

### *1.3.2. ANALGESIC EFFECTS (REF. 4, 9, 12, 21)*

The analgesic actions of celecoxib (SC-58635) were evaluated in various models and findings are presented in the following table.

| Hyperalgesia Models | Species | Dose(mg/kg)/Route | Observations |
|---|---|---|---|
| Carrageenan Induced Hyperalgesia (Hargreave's) | SD rats | 3, 10, 30, 50, 100 po | Dose-dependent ↓ with an $ED_{50}$ of 0.35 mg/kg. |
| Formalin Model | Swiss-Webster mice | 10, 30, 50 po | ↓ 67% and 88% at levels of 30 and 50 mg/kg, respectively |
| Phenyl Benzoquinone (PBQ)-Induced Doxoflexion | Swiss-Webster mice | 5 po | ↓ 56% of dorsoflexion response |
| Acetic Acid-Induced Writhing | ♂ ICR mice | 50, 150 and 500 po | Dose-dependent ↓ the number of dorsoflexions by 54.1, 91.2 and 95.1%, respectively. |

### *1.3.3. ANTIPYRETIC EFFECTS (REF. 7)*

The effects of celecoxib on LPS-induced fever were evaluated in rats. Basal body temperature was taken rectally 1 hr prior to ip injection of LPS or saline and then animals were immediately treated intragastrically with 30 mg/kg SC-58635 or 10 mg/kg indomethacin or vehicle immediately post-LPS stimulation. Body temperature was measured at 1 hr intervals for 5 hr post-LPS.
Results showed that oral application of SC-58635 (30 mg/kg) reduced LPS-induced fever in rat by 42% but did not alter normal body temperature.

### *1.3.4. CHEMOPREVENTION OF AZOXYMETHAN-INDUCED COLONIC ABERRANT CRYPT FOCI (ACF) AND TUMOR (REF. 22, 23)*

#### 1.3.4.1. Inhibition of Azoxymethan-Induced Colonic Aberrant Crypt Foci (Ref. 22)

Animals: ♂ F344 rats (Charles River), 5 weeks old

Designs: Groups of rats were fed with either control diet or diet containing SC-58635 , Sulindac or placebo for 12 weeks (5-16 weeks of age). Two weeks after placing on diet containing SC-58635, Sulindac or vehicle, all but control rats were given with azoxymethan (AOM), 15 mg/kg, or saline sc 1x/week for 2 weeks. Animals were sacrificed at 16 weeks of age, the colons were removed and fixed in 10% formalin. Microscopic evaluations were performed and ACF were recorded.

**Results:** Comparable body weights were obtained for each group. No apparent gross pathological changes were noted in the liver, kidney, GI, and lung. The effects of feeding SC-58635 and Sulindac on AOM-induced ACF formation (mean ± SD) are presented in the following table. No evidence of ACF formation in the colon of animals treated with salinewa noted.

| Treatment Groups (n=12) | | AOM-Treatment | Total Nº of ACF/rat | Nº of Foci Containing | | | |
|---|---|---|---|---|---|---|---|
| | | | | 1 Crypt | 2 Crypts | 3 Crypts | 4 Crypts |
| Control Diet | | + | 120 ± 15 | 16 ± 6.5 | 35 ± 7.7 | 34 ± 4.6 | 35 ± 7.9 |
| SC-58635 | 1500 ppm | + | 71 ± 15** | 10 ± 4.5* | 22 ± 6.8** | 20 ± 6.8** | 18 ± 5.8** |
| | 150 ppm | + | 127 ± 13 | 16 ± 4.6 | 44 ± 7.0 | 35 ± 6.8 | 33 ± 6.6 |
| Sulindac | 320 ppm | + | 77 ±14** | 11 ± 6.3* | 24 ± 8.5** | 21 ± 6.6** | 21 ± 5.8** |
| Placebo | 1500 ppm | + | 111 ± 35 | 15 ± 7.7 | 34 ± 11.8 | 31 ± 10.1 | 31 ± 10.2 |

** p≤0.001; * p≤0.05.

1.3.4.2. Inhibition of Azoxymethan-Induced Colonic Tumors (Ref. 23)

Animals: ♂ F344 rats (Charles River), 5 weeks old

Designs: Groups of rats were fed with either control diet or diet containing 1500 ppm of SC-58635 for ≥ 52 weeks. Two weeks after placing on diet containing SC-58635 or control diet, all but control rats were given with azoxymethan (AOM), 15 mg/kg, or saline sc 1x/week for 2 weeks. Body weights were recorded 1x/week for the 1st 8 weeks and 1x/4weeks thereafter. Animals were sacrificed 50 weeks after the second AOM injection. The GIs were removed and tumors (size, location and number) were recorded.

**Results:** Comparable body weights were obtained for each treatment group. No apparent gross or histopathological changes were noted in the liver, kidney, GI, and lung. The effects of feeding SC-58635 on the incidence of AOM-induced colon tumors, tumor size and tumor volume are shown in the following table. No evidence of colon tumors was noted in animals that were placed on either control or SC-58635 containing diet (9/group) treated with saline.

| Treatment | AOM | Type of Tumors | | Incidence (%) | Multiplicity (Nº of tumors/rat) | Tumor Size (mm)/ Nº of Tumors | | Tumor Volume ($mm^3$) |
|---|---|---|---|---|---|---|---|---|
| Control Diet (N=36) | + | Adenoma | | 9 | 0.09 ± 0.28[a] | <5 | 36 | |
| | | Adenocarcinoma | Non-invasive | 41 | 0.59 ± 0.77 | 5-10 | 17 | |
| | | | Invasive | 76 | 1.26 ± 1.01 | >10 | 10 | |
| | | Total | | 85 | 1.91 ± 1.38 | | | 204 ± 483 |
| SC-58635 (1500 ppm) (N=36) | + | Adenoma | | 0 | 0 | <5 | 1 | |
| | | Adenocarcinoma | Non-invasive | 3* | 0.03 ± 0.16* | 5-10 | 0 | |
| | | | Invasive | 3** | 0.03 ± 0.16** | >10 | 1 | |
| | | Total | | 6** | 0.06 ± 0.23** | | | 27 ± 23 |

[a] Values expressed as mean ± SD; **p≤0.000001; *p≤0.001.

## 1.4. SAFETY PHARMACOLOGY (REF. 5, 18-21, 24-29)

Reports related to safety pharmacology were summarized in the following table.

| STUDY TYPE | | SPECIES | DOSE/ROUTE | RESULTS |
|---|---|---|---|---|
| **Effect on General Activity and Behavior** | | | | |
| General Activity and Behavior | | Mice, 3/group | 0, 50, 150, or 500 mg/kg po | 50 & 150 mg/kg: slightly ↓ locomotive activities.<br>500 mg/kg: ↑ in locomotive activities in ⅓ mice. |
| **Effect on Central Nervous System** | | | | |
| Spontaneous Locomotor Activity | | Mice, 10/group | 0, 50, 150, or 500 mg/kg po | 500 mg/kg: significantly ↓ spontaneous locomotive activities by 87% as compared to control animals at 3 hr post dosing. |
| Effect on Hexobarbital-Induced Sleep | | | | ↑ hexobarbital-induced sleep dose-dependently |
| Electroshock-Induced Convulsions | Synergestic | | | ≥150 mg/kg: slightly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected. |
| | Antagonistic | | | ↓ incidences of tonic convulsions dose-dependently, the incidences of clonic and mortality were not affected. |
| Chemical-Induced Convulsions | Synergestic | | | ≥150 mg/kg: significantly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected. |
| | Antagonistic | | | dose-dependently ↓ the incidences of tonic convulsions and mortality, the incidences of clonic were not affected. |
| Analgesic Activity | | | | Significantly ↓ acetic acid-induced writhing in dose-dependent fashion, but had no effect on tail pinch-induced pain. |
| Body Temperature | | Rat, 8/group | 0, 50, 150, or 500 mg/kg po | ↔ |
| **Effect on Autonomic Nervous System and Smooth Muscle** | | | | |
| Spontaneous Motility | | Guinea Pig Isolated Ileum | $4x10^{-8}$ to $4x10^{-5}$ M | ≥$4x10^{-6}$: significantly ↓ the amplitude of spontaneous motility |
| Agonist-induced Contraction | | | | ≥$4x10^{-7}$ M: ↓ $BaCl_2$-induced contractions; ≥$4x10^{-6}$ M: ↓5-HT-induced contractions; ≥$4x10^{-5}$ M: ↓ ACh-, Histamine-induced contractions. |
| **Effect on Digestive system** | | Mice, 10/group | 0, 50, 150, or 500 mg/kg po | ↔ on the rate passage of charcoal meal in small intestine. |
| **Effect on Respiratory and Cardiovascular Systems** | | Dog, 3/group | 0, 50, 100 or 200 mg/kg | 200 mg/kg: ↑ blood flow significantly,<br>↔ on the ECG, and PR, QT, and QRS interval times, systolic, diastolic, and mean blood pressure, heart rate and respiratory pressure |
| **Effect on Urine Volume, Urinary $PGE_2$, and Urinary Electrolytes Excretion** | | Rat, 8/group | 0, 50, 150, or 500 mg/kg po | ↓ urine volume significantly up to 6 hr postdose, and $Na^+$, $Cl^-$ excretion;<br>↑ urinary osmolarity significantly;<br>↔ on $K^+$ excretion and pH. |
| | | | 0, 5, 15, 50, mg/kg po | 50 mg/kg: similar effects were obtained as previous test.<br>15 mg/kg: ↓ urine volume at 3 hr postdose; ↑ urinary osmolarity for 6 hr, excretion of urine electrolytes were not affected. |
| | | ♂ Rat, 6/group | 600 mg/kg/day x7 | ↔ urine volume, urinary $PGE_2$<br>↓ kidney $PGE_2$ |
| | | ♀ Rat, 8/group | 600 mg/kg/day x3 or x7 | ↔ urine volume, urinary $PGE_2$ |

## 1.5. REFERENCES

The following pharmacology study reports or published manuscripts were submitted in current NDA.

# 2. TOXICOLOGY

## 2.1. ACUTE (SINGLE DOSE) TOXICITY STUDIES

2.1.1.1. A Single Dose Oral Toxicity Study Of SC-58635 In The Rat Document No.: SBL 77-64; Date:29-Sep-1995 (Vol. 1.10, p. 1-30)

| | |
|---|---|
| Study Nº: | SBL 77-64 |
| Study Aims: | To determine acute toxicity of SC-58635 in rats. |
| Compound: | SC-58635 (Lot Nº 94K031-A2A |
| Vehicle: | 0.5% methylcellulose and 0.1% polysorbate 80 aqueous solution |
| Dose and Route: | 0, 1000, or 2000 mg/kg po by gavage |
| Animals: | SPF Crj:CD(SD) rats, 5 weeks of age, weighing g for ♂ and g for ♀, 5/sex/group. |
| Study Date: | 4/26/95 - 9/29/95 |
| Study Site: | |
| GLP/AUC: | Yes |

Study Design: Rats were orally dosed with SC-58635 in 0.5% methylcellulose and 0.1% polysorbate 80 aqueous solution at doses of 0, 1000, or 2000 mg/kg. Animals were monitored for 14 days. The following observations were performed:

- Clinical Signs and Mortality - 2x/day;
- Body Weight- Days 0, 1, 4, 8, and 13;
- Necropsy - Day 14. All organs and tissues were examined macroscopically. Histopathology Examination: Histopathology examinations were not performed, as no abnormalities were observed in the gross pathology examination. The liver and kidneys were fixed in 10% neutral buffered formalin and stored.

**Results:**

- Clinical Signs and Mortality - No deaths occurred. White stool was seen in 4♂ and 5♀ @ 2000 mg/kg on the day of dosing.
- Body Weight - Normal.
- Necropsy - No remarkable abnormalities were seen.

2.1.1.2. A Single Dose Oral Toxicity Study Of SC-58635 In The Dog, Document No.: SBL 77-63; Date:29-Sep-1995 (Vol. 1.10, p. 31-62)

| | |
|---|---|
| Study Nº: | SBL 77-63 |
| Study Aims: | To determine acute toxicity of SC-58635 in male beagle dogs. |
| Compound: | SC-58635 (Lot Nº 94K031-A2A |
| Vehicle: | Empty gelatin capsule |
| Dose and Route: | 1000 and 2000 mg/kg po |
| Animals: | ♂ beagle dogs, month-old, weighing kg, 2/group |
| Study Date: | 4/26/95 - 9/23/95 |
| Study Site: | |
| GLP/AUC: | Yes |

Study Design: ♂ beagle dogs (2/group) were given a single oral dose of SC-58635 in gelatin capsules at doses of 0, 1000, or 2000 mg/kg. Animals were observed for 14 days. The following observation were performed:

- Clinical Signs and Mortality - 2x/day;
- Food Consumption - 1x/day;
- Body Weight - Days 0, 1, 4, 8, and 13;
- Heart Rate & Body Temperature - Days 0, 1, 4, 8, and 13
- Necropsy - Day 14. All organs and tissues were examined macroscopically.
  Organ Weight (absolute and relative): brain (including cerebellum and brain stem), pituitary, thyroids (including parathyroid, weighed after preservation in formalin), submandibular glands, thymus, heart, lungs (including bronchus), liver, adrenals, kidneys, spleen, stomach, testes, epididymides, prostate and urinary bladder
  Histopathology Examination: Histopathology examinations were not performed, as no abnormalities were observed in the gross pathology examination. The heart, spleen, thymus, lungs, bronchus, stomach (fundus, pylorus), small intestine (duodenum, jejunum, ileum), large intestine (cecum, colon, rectum), liver, kidneys and urinary bladder were fixed in 10% neutral buffered formalin and stored.

**Results:**

- Clinical Signs and Mortality - Vomiting was noted in one each animal at 1000 and 2000 mg/kg immediately after dosing and these dogs had test article like substance in the stool on the day of dosing.
- Food Consumption and Body Weight - Normal.
- Heart Rate and Body Temperature - A slight ↓ in heart rate was noted for 6 hours in one dog @ 2000 mg/kg on Day 0 post dosing.
- Necropsy - No abnormalities were observed.

2.1.1.3. Acute Limits Of Lethality Study Of SC-58635 In The Cynomolgus Monkey, Document No.: PSA95S-30-SA4350; Date: 16-May-1995 (Vol. 1.10, p.63-118)

Study Nº: SA4350
Report Nº: PSA-95S-30-4350
Study Aim: To evaluate the acute lethal dose SC-58635 after single oral administration
Compound: SC-58635 (Lot Nº 94K014-A2B, 100% free compound) suspensions in 0.5% methylcellulose and 0.1% Tween® 80, 10 mg/ml
Dosage & Route: 25 and 250 mg/kg, 5 ml/kg po
Animals: ♀ Charles River cynomolgus monkeys, years of age, weighing <g, 3/group
Study Location: G.D. Searle, Skokie, IL
Study Date (In-Life): 2/10/95 - 2/23/95
Compliance with GLP/QAU: Yes

Study Design: Animal grouping and dose allocations are presented in the following table. All animals were monitored for mortality, general appearance and behavior daily. Body weight of each animal was measured on day -1, and day 1 prior to dosing, and on Day 14. Plasma samples were obtained from each animal at 3 and 24 hr after dosing on Day 1 for PK analysis. Necropsies were not performed and all animals were returned to the animal stock pool at the end of experiment.

| Group | Treatment | Dose (mg/kg/day) | Nº of Animals |
|---|---|---|---|
| 1 | SC-58635 | 25 | 3 ♀ |
| 2 | SC-58635 | 250 | 3 ♀ |

**Results:** No deaths occurred during the experiment; therefore, the $LD_{50}$ of SC-58635 for ♀ cynomolgus monkeys appeared to be >250 mg/kg. Watery stool was observed on Day 1 in one animal from both treatment groups. The one receiving 25 mg/kg/day also showed blood in the stool on Day 2; she appeared to be normal on Days 3-14. Some other animals in either groups had soft or watery stools on Days 7-14. Body weights of all animals were not modified by SC-58635. The mean concentrations of SC-58635 in ♀ cynomolgus monkeys 3 and 24 hr post dosing with 25 and 250 mg/kg/day were presented in the following table.

| Treatment Dose (mg/kg/day) | Plasma SC-58635 Levels (μg/ml) | |
|---|---|---|
| | 3 hr | 24 hr |
| 25 | 0.140 ± 0.016 | 0.0355 ± 0.0077 |
| 250 | 0.521 ± 0.136 | 0.144 ± 0.025 |



## 2.2. REPEATED DOSE TOXICITY STUDIES

### *2.2.1. SUBCHRONIC TOXICITY STUDIES*

**MOUSE STUDIES**

2.2.1.1. Two-Week Feasibility Study Of SC-58635 Dietary Admix In The Mouse (EX 4325) Document No.: P30E4325; Date: 17-Sep-1996 (Vol. 1.11, p. 1-315)

Included as an appendix to this report was:
Analysis Of Plasma SC-58635 Concentrations In A Two-Week Feasibility Study Of SC-58635 Dietary Admix In The Mouse, EX4325, Document No.: MRC-95S-0098; Date: 24-May-1995

Report Nº: P30E4325 & MRC-95S-0098 (PK Study)
Study Nº: EX4325
Study Aim: To evaluate the feasibility of dietary admix as a means of SC-58635 dose administration for future long term toxicity studies.
Compound: SC-58635 (Lot Nº 94K014-A4A) mixed with basal diet
Dose & Route: 0, 100, 300, 1000, 3000 mg/kg/day for the toxicology study, and 100, 300 & 1000 mg/kg/day for the companion PK study

| Toxicology Study | | | | Satellite PK Study | | | |
|---|---|---|---|---|---|---|---|
| Group | Dose (mg/kg/day) | Nº of Animals | Necropsy | Group | Dose(mg/kg/day) | Nº of Animals | Necropsy |
| 1 | 0 | 10/sex | 10/sex | 6 | 100 | 15/sex | 0/sex |
| 2 | 100 | 10/sex | 10/sex | 7 | 300 | 15/sex | 0/sex |
| 3 | 300 | 10/sex | 10/sex | 8 | 1000 | 15/sex | 0/sex |
| 4 | 1000 | 10/sex | 10/sex | | | | |
| 5 | 3000 | 10/sex | 10/sex | | | | |

Animals: ♂ & ♀ CD-1 Mice, ~6 weeks of age, weighing g for ♂ and g for ♀, 10/sex/group for the toxicology study and 15/group for the PK study
Study Location: G.D. Searle & CO., 4901 Searle Parkway, Skokie, IL 60077
Study Date (In-Life): 01/12/95 - 01/26-27/95
Compliance with GLP/QAU: Not Indicated
Study Design: SC-58635 was given to toxicology study mice in the diet for ≥14 days and PK study mice for ≥13 days. Animals were observed 1x daily for mortality and moribundity. Physical examinations were performed on each animal on Days -7, 1, 7, and 14. Body weights were recorded 2x prior to treatment and 2x/week during treatment. Food consumption was measured for 2 consecutive days before the study and 2x/week during treatment. Serum samples were collected from 5 animals/sex in Groups 1, 2, 3, and 4 for clinical chemistry parameter evaluation on Day 15. Blood was obtained from 5 animals/sex in Groups 1, 2, 3, and 4 for hematology analysis on Day 16. The hematology and clinical chemistry parameters evaluated are listed in the following table.

Scheduled necropsy was performed on Day 15 or Day 16 and microscopic evaluations were performed on specified organs as shown in the following table. For the PK parameter determination, blood samples were collected from 3 animals/sex each in groups 6, 7, and 8 on Days 13 and 14.

| HEMATOLOGY | | | | HISTOPATHOLOGICAL EVALUATIONS | |
|---|---|---|---|---|---|
| White Blood Cells (WBC) | Mean Corpuscular Volume (MCV) | | | Brain | Stomach |
| Differential White Blood Cells | Mean Corpuscular Hemoglobin (MCH) | | | *Heart | *Testes (Both) |
| Red Blood Cells | Mean Corpuscular Hemoglobin Concentration (MCHC) | | | *Kidneys (Both) | *Thymus |
| Hemoglobin (Hb) | Platelets | | | *Liver | Intestinal Tract |
| Hematocrit (Ht) | Mean Platelet Volume | | | Lung | Gross Lesions |
| CLINICAL CHEMISTRY | | | | | |
| ALT | Calcium | Globulin | Sodium | Total Protein | |
| Albumin | Chloride | Glucose | Sorbitol Dehydrogenase | Triglycerides | |
| Alkaline Phosphatase | Cholesterol | Inorganic Phosphorus | Total Bile Acids | Urea | |
| AST | Creatinine | Potassium | Total Bilirubin | | |

* Organs were weighed. Paired organs were weighed together.

**Results:**

- Dosage Concentration Determination - Dosages were calculated using body weight data, food consumption measurements and dose formulation information, and the actual dosages for each group are given in the following table.

| Group | Intended Dose (mg/kg/day) | Actual Dose (mg/kg/day) ♂ | ♀ |
|---|---|---|---|
| 2 | 100 | | |
| 3 | 300 | | |
| 4 | 1000 | | |
| 5 | 3000 | | |



- Clinical Signs and Survivals - Hunched posture, shivering, reduced activity, higher incidence of ventral staining, and reduce number of feces were major clinical signs seen in SC-58635 treated mice. The mortality or moribundity for each group is shown in the following table.

| Group | Dose (mg/kg/day) | Died/Moribund Sacrifice ♂ | ♀ |
|---|---|---|---|
| 1 | 0 | 0/10 | 0/10 |
| 2 | 100 | 0/10 | 0/10 |
| 3 | 300 | 1/10 | 0/10 |
| 4 | 1000 | 2/10 | 0/10 |
| 5 | 3000 | 6/10 | 2/10 |



- Food Consumption and Body Weight - Significant reductions in mean body weights with reduced food consumption were noted for ♂ @ ≥1000 mg/kg and ♀ @ 3000 mg/kg/day as shown in the following table. Weight loss (negative weight gains) was noted in high dose group.

| Parameter | Trt. Day | 1000 mg/kg ♂ | 1000 mg/kg ♀ | 3000 mg/kg ♂ | 3000 mg/kg ♀ |
|---|---|---|---|---|---|
| Mean Body Weight | Day 5 | ↓4.7% | NS | ↓21.7% | ↓7.5% |
| | Days 8-14 | ↓4.6 - 9% | NS | - | ↓9.4% |
| Mean Food Consumption | Days 1-5 | - | ↓20% | ↓62.3% | ↓45.3% |
| | Days 5-8 | ↓27.8% | ↓14.9% | - | ↓38.3 |
| | Days 8-12 | ↓21.8% | ↓8.2% | - | - |
| | Days 12-14 | ↓19.2% | ↓12.5% | - | - |

NS = Non-significant; - = No data available.

- Clinical Pathology - Males @ 1000 mg/kg/days had ↓ (18.4%) serum albumin levels and slightly ↑ ALT values (1.55x). No remarkable findings were observed in hematological analyses.
- Gross Pathology - A slight ↑ in liver/body weight ratios was noted in both ♂ & ♀ receiving 1000 mg/kg/day SC58635. Gastrointestinal erosions/ulcers with secondary peritonitis and discolored kidney were major macroscopic changes seen in animals that died or were

sacrificed at moribund. Gross changes found in mice at terminal necropsy were an ulcer in jejunum with fibrinous peritonitis in one ♂ @ 1000 mg/kg and a well demarcated, tan region in the cranial pole of the left kidney in one ♀ @ 1000 mg/kg/day.

- Histopathology - Macro- and micro-scopic examinations were not done on the samples from mice receiving 3000 mg/kg/day. Microscopic lesions found in the mice that died or were sacrificed at moribund included renal papillary necrosis, multiple small foci of transmural necrosis and inflammation with secondary peritonitis and thymic atrophy. Test article-related microscopic changes found in the terminal sacrificed animals (♂ @ ≥300 mg/kg/day and ♀ @ 1000 mg/kg/day) were restricted to the stomach, small and large intestines and kidneys. Pathological changes in the GI were similar to those seen in the mice that died or were sacrificed at moribund. Renal injury with characteristics of focal degeneration of renal tubules with regeneration, epithelial basophilia, intralumental casts (hyaline or cellular) and a minimal mononuclear cell infiltration was seen in 3♂ and 4♀ @ 1000 mg/kg.
- PK - Mean PK parameters for SC58635 on following oral administration to mice via dietary admix for 2-week are presented in the following table. AUC and $C_{max}$ values were higher in males than females. A dose proportional increase in AUC and $C_{max}$ values was noted in ♀ @ all dose levels and ♂ @ 100 and 300 mg/kg/day.

| Dose (mg/kg/day) | $C_{max}$ (μg/ml) | | $T_{max}$ (hr) | | $AUC_{0-24}$ (μg•hr/ml) | |
|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| 100 | 3.52 | 1.52 | 6 | 6 | 55.8 | 20.4 |
| 300 | 10.4 | 4.54 | 6 | 24 | 148 | 60.5 |
| 1000 | 19.7 | 10.6 | 6 | 24 | 288 | 162 |



Based upon the findings of the present study, the NOAEL of SC-58635 in dietary admix was 100 and 300 for ♂ and ♀ mice, respectively. GI (perforated ulcers with secondary peritonitis) and kidney (renal tubule degeneration/regeneration) were the major target organs.

2.2.1.2. Thirteen-Week Range-Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse (EX4357) Document No: P30E4357; Date: 29-Apr-1996 (Vol. 11.17-1.18)

Included as an appendix to this report were:

1. Analysis Of Plasma SC-58635 Concentrations In A Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4537, Document No.: MRC95S-30-950208; Date: 07-Sep-1995
2. Final Report Amendment No. 1: Analysis Of Plasma SC-58635 Concentrations In a Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4357, Document No.: M3195208; Date: 11-Mar-1996
3. Final Report Amendment No. 2: Analysis Of Plasma SC-58635 Concentrations In a Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4357, Document No.: M3295208; Date: 18-Nov-1996
4. Final Report Amendment No. 3: Analysis Of Plasma SC-58635 Concentrations In a Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4357, Document No.: M3395208; Date: 21-Jul-1997
5. Final Report Amendment No. 1: Thirteen-Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse (EX4357), Document No.: P31E4357; Date: 14-Oct-1997

| | |
|---|---|
| Report Nº: | P30E4357 & MRC95S-30-950208 (PK Study) |
| Study Nº: | EX4357 |
| Study Aim: | To evaluate the toxic effect of SC-58635 in the mouse and to select dosages for a carcinogenicity study in the mouse. |
| Compound: | SC-58635 (Lot Nº 94K014-A3B) mixed with basal diet |

Dose & Route: 0, 75, 150 & 300 mg/kg/day for ♂ study, and 0, 150, 300 & 1000 mg/kg/day for the ♀ study.

Animals: ♂ & ♀ CD-1 Mice, ~5 weeks of age, weighing g for ♂ and for ♀, 20/sex/group for the toxicology study and 90/sex/group for the PK study

Study Location: G.D. Searle & CO., 4901 Searle Parkway, Skokie, IL 60077

Compliance with GLP/QAU: No.

Study Date: 3/28/95 to 6/27-29/95

Study Design: Male and female CD-1 mice were randomly assigned to one of 7 dose groups as shown in the following table.

| Toxicology Study Group | | PK Study Group | | Intended Dose (mg/kg) | | Actual Dose (mg/kg) | |
|---|---|---|---|---|---|---|---|
| Group Nº | Nº of Animals | Group Nº | Nº of Animals | ♂ | ♀ | ♂ | ♀ |
| 1 | 20/Sex | | | 0 | 0 | 0 | 0 |
| 2 | 20/Sex | 5 | 90/sex | 75 | 150 | 70.7 - 78.90 | 148 - 167 |
| 3 | 20/Sex | 6 | 90/sex | 150 | 300 | 139 - 163 | 248 - 329 |
| 4 | 20/Sex | 7 | 90/sex | 300 | 1000 | 290 - 321 | 888 - 1103 |

The following observations were performed.

- Mortality and Clinical Signs - 2x/week day, 1x/weekend day.
- Physical Examination - 1x pretest and 1x/week.
- Body Weight & Food Consumption - 1x/week.
- Hematology & Clinical Chemistry - Week 14; 10 animals/sex from Groups 1-3, and 10 ♂ from Group 4.
- Toxicokinetics - Days 1/2, 45/46, and 87/88.
- Necropsy & Histopathology - Days 92-94. Tissues from Group 4 females were not examined microscopically.

**Results:**

- Mortality and Clinical Signs - Totals of 18 animals in the Toxicology Study, Groups 1-5, and 29 animals in the PK study, Groups 5-7, were found dead or sacrificed at moribund condition. Mortality data for each group are shown in the following table. Most of the deaths or moribundity were due to SC-58635 treatment related GI toxicity and secondary peritonitis. For the toxicology study animals, the cause of death for one each ♀ at 0, 150 and 1000 mg/kg/day could not be determined and accidental death was found in one ♀ at 0 and 150 mg/kg. As for the PK study animals, death attributable to test article-related GI injury and/or peritonitis was noted for one ♂ @ 75 mg/kg, one ♂ @ 150 mg/kg/day, 5♂ & 1♀ @ 300 mg/kg/day and 15♀ @ 1000 mg/kg/day. Animals at the state of moribund had signs of hunched posture, tremors/shivering, reduced activity, motor incoordination, and cold to touch.

| Group | ♂ | | ♀ | |
|---|---|---|---|---|
| | Dose (mg/kg/day) | Died/Moribund Sacrifice | Dose (mg/kg/day) | Died/Moribund Sacrifice |
| 1 | 0 | 0/20 | 0 | 2/20 |
| 2 | 75 | 0/20 | 150 | 2/19 |
| 3 | 150 | 2/20 | 300 | 2/20 |
| 4 | 300 | 3/20 | 1000 | 7/19 |
| 5 | 75 | 1/60 | 150 | 0/60 |
| 6 | 150 | 2/60 | 300 | 1/60 |
| 7 | 300 | 7/60 | 1000 | 18/59 |



- Body Weight & Food Consumption - Groups 3 and 4 ♀ had significant ↓ (5-10%) in mean body weights and cumulative weight gains starting at Week 5 or Week 6. Females @ 1000 mg/kg/day had a significant reduction in food consumption at Weeks 3, 4, 7, and 11 with values of 85-94% of the control values.

- Hematology & Clinical Chemistry - A dose-dependent ↓ in serum triglycerides was noted in both sexes @ ≥150 mg/kg/day.
- Toxicokinetics - SC-58635 was absorbed systemically following oral dietary administration. It appeared that plasma levels of SC-58635 increased proportionally as the dose increased.

| Parameters | | | Dose Levels (mg/kg) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 75 | 150 | | 300 | | 1000 |
| | | | ♂ | ♂ | ♀ | ♂ | ♀ | ♀ |
| $C_{max}$ (μg/ml) | Day | 1 | 2.78 | 6.71 | 2.99 | 12.8 | 6.22 | 14.6 |
| | | 45 | 2.0 | 4.62 | 1.92 | 8.27 | 2.79 | 12.8 |
| | | 87 | 2.44 | 3.79 | 2.04 | 6.65 | 3.55 | 11.5 |
| $AUC_{0-24}$ (μg•hr/ml) | Day | 1 | 38.7 | 84.7 | 42.1 | 216 | 85.3 | 226 |
| | | 45 | 32.2 | 70.7 | 24.2 | 153 | 47.0 | 181 |
| | | 87 | 39.6 | 57.2 | 30.8 | 123 | 48.0 | 183.0 |
| $T_{max}$ (hr) | Day | 1 | 15 | 15 | 12 | 18 | 12 | 6 |
| | | 45 | 9.0 | 9.0 | 9.0 | 18 | 9.0 | 9.0 |
| | | 87 | 12.0 | 12.0 | 9.0 | 9.0 | 9.0 | 9.0 |



- Gross Pathology Histopathological Findings -
  Unscheduled Deaths: The incidence of unscheduled dead (sacrificed moribund or found dead) animals with treatment-related gastrointestinal lesions (perforated ulcers and secondary fibrinous peritonitis) is shown in the following table.

| Group | ♂ Died/Moribund Sacrifice | | ♀ Died/Moribund Sacrifice | |
|---|---|---|---|---|
| | Dose (mg/kg/day) | GI Lesions | Dose (mg/kg/day) | GI Lesions |
| 1 | 0 | 0/20 | 0 | 0/20 |
| 2 | 75 | 0/20 | 150 | 0/19 |
| 3 | 150 | 2/20 | 300 | 2/20 |
| 4 | 300 | 3/20 | 1000 | 7/19 |
| 5 | 75 | 1/60 | 150 | 0/60 |
| 6 | 150 | 1/60 | 300 | 1/60 |
| 7 | 300 | 5/60 | 1000 | 15/59 |



Terminal Sacrifice: Treatment-related macro- and micro-scopic findings were restricted to the GI tract. In the gross examination, gastrointestinal hemorrhage or mucosal injury were noted in 2/18 ♂ @ 150 and 1/17♂ @ 300 mg/kg/day and black GI contents suggestive of intralummental hemorrhage were observed in 1♀ @ 300 mg/kg. Microscopic lesions including ulceration of the stomach and ileum, inflammation of gastric submucosa, transmural inflammation of the stomach and jejunum, and secondary peritonitis were identified in 1/20 ♂ @ 75, 2/18 ♂ @ 150, and 4/17 ♂ and 1/19 ♀ @ 300 mg/kg/day. A slight → mild nephropathy with characteristics of focal loss of tubule with tubular regeneration, occasional hyaline or cellular cast, and slight to mild mononuclear cell interstitial infiltration were noted in all groups of animals.

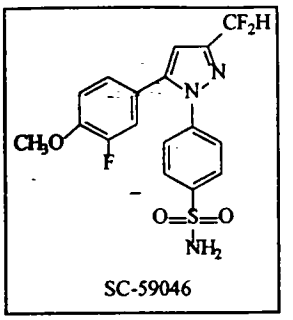
Therefore, the NOAEL for ♀ mice was 150 mg/kg/day. The NOAEL was not established for ♂ mice. GI (perforated ulcers with secondary peritonitis) was the major target organ. Inconclusive nephropathy was noted.

RAT STUDIES

2.2.1.3. Range-Finding Toxicity Study (Escalating Dose Design) with SC-58635, SC-58553, SC-59046 And SC-58994 In Rats, Document No.: PSA95S-30-EX4219; Date: 20-Mar-1995 (Vol. 1.12, p. 1-335)

Included as an appendix to this report was:
Plasma Concentration Data From The 15-Day Escalating Dose Toxicity Study Of SC-58635 In The Rat, EX4219, Document No.: MRC-94S-0207; Date: 13-Feb-1995

Study Nº SA4219
Report Nº PSA-95S-30-4219
Study Aim: To identify potential target organs or dose limiting toxicities and evaluate for tolerance following repeated dosing of SC-58635 and SC-59046 in rats
Compound: SC-58635 (Lot Nº GDS-2977-158) & SC-59046 (Lot Nº GDS-3196-095) in 1.5% methylcellulose and 0.1% Tween 80; 10, 20, 40 60, and 80 mg/ml
Dosage & Route: 100, 200, 400 600 and 800 mg/kg, 10 ml/kg oral (by gavage)
Control Vehicle: 1.5% methylcellulose + 0.1% Tween 80
Animals: 30♂ & 30♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR, 5 wk of age, weighing from g for Phase I study and g for Phase II study, 5 sex/group
Study Location: G.D. Searle, Skokie, IL
Compliance with GLP/QAU: No



SC-59046

Study Design:

**Phase I:** SC-58635 and SC-59046 were given to rats (5 sex/group) orally by gavage using a dosing schedule, as shown in the following table, with 3 day escalation intervals at an initial dose level of 100 mg/kg, until a maximum dose level of 800 mg/kg reached.

**Phase II:** SC-58635 and SC-59046 at levels of 600 & 800 mg/kg were orally administered to rats (3/sex/group) by gavage daily for 3 days.

| PHASE I (DOSE ESCALATION) | | | | |
|---|---|---|---|---|
| Group | Treatment | Dose (mg/kg/day) | Treatment Days | Nº of Animals |
| 1 | Vehicle Control | - | 1 - 15 | 5/sex |
| 2 | SC-58635 | 100 | 1 - 3 | 5/sex |
| | | 200 | 4 - 6 | |
| | | 400 | 7 - 9 | |
| | | 600 | 10 - 12 | |
| | | 800 | 13 - 15 | |
| 3 | SC-59046 | 100 | 1 - 3 | 5/sex |
| | | 200 | 4 - 6 | |
| | | 400 | 7 - 9 | |
| | | 600 | 10 - 12 | |
| | | 800 | 13 - 15 | |
| **PHASE II** | | | | |
| Group | Treatment | Dose (mg/kg/day) | Treatment Days | Nº of Animals |
| 1 | Vehicle Control | - | 1 - 3 | 3/sex |
| 2 | SC-58635 | 600 | 1 - 3 | 3/sex |
| 3 | SC-58635 | 800 | 1 - 3 | 3/sex |
| 4 | SC-59046 | 600 | 1 - 3 | 3/sex |
| 5 | SC-59046 | 800 | 1 - 3 | 3/sex |



The animals were observed daily approximately 1-4 hr post dosing for clinical signs and mortality. Body weights were recorded once during pretreatment and daily during the treatment period; feed consumption was measured every 3 days. Hematological and clinical chemistry examinations, necropsy were performed on fasted animals (16 hr prior to scheduled necropsy) on Day 16 for Phase I and Day 4 for Phase II studies. The hematological and blood chemistry parameters analyzed and organs collected are shown in the following table. PK sampling were performed on Days 3, 6, 9, 12, 15, and 16 for Phase I and Days 3 and 4 for Phase II experiments. Macro- and micro-histological (only representative samples from Phase I study) examinations were also conducted.

| HEMATOLOGY | | SERUM CHEMISTRY | | | |
|---|---|---|---|---|---|
| *White Blood Cells | MCV | *ALT | *Chloride | Inorganic Phosphorus | *Total Bilirubin |
| *Differential WBC | MCH | *Albumin | Cholesterol | *Potassium | Total Protein |
| Red Blood Cells | MCHC | Alkaline Phosphatase | Creatinine | *Sodium | Triglycerides |
| Hemoglobin | Mean Platelet Volume | AST | Globulin | *Sorbitol Dehydrogenase (SDH) | |
| *Hematocrit | Platelets | Calcium | Glucose | Total Bile Acids (TBA) | *Urea |
| *If the sample size from an animal was insufficient to measure all of the parameters listed above, the parameters marked with an asterisk were measured first. Non-asterisk parameters were measured in the order listed as the sample size permitted. | | | | | |

| ORGAN COLLECTED IN PHASE I STUDY | | |
|---|---|---|
| *Brain | *Liver | *Stomach |
| *Heart | *Lungs | *Testes (Both) |
| Intestine, Small (Duodenum, Jejunum, Ileum) | Lymph Node (Submaxillary and Mesenteric) | *Thymus |
| Intestine, Large (Cecum, Colon) | Pancreas | *Thyroid Glands** (both) |
| *Kidneys (both) | *Spleen | Urinary Bladder |

* Tissues designated with an asterisk were weighed. Paired organs were weighed together.
** The parathyroids were weighed with the thyroids and were examined microscopically if they were included in the thyroid sections.

**Results:**

- Clinical Observations and Mortality - Mild hair loss and skin abrasions were periodically identified and these findings might not be treatment related. No deaths occurred in either Phase I or II of this study.
- Body Weights and Food Consumption - There were no differences in body weights and mean body weight gains in Phase I study. In Phase II study, mean body weights of males receiving 800 mg/kg of SC-59046 and females receiving either 600 or 800 mg/kg of SC-59046 were and less than controls, respectively. Mean body weight gains of animals @ 600 or 800 mg/kg of SC-59046 were less than controls. Significantly higher mean feed consumption was seen in Phase I females given SC-58635 during Days 1-7 (↑ 10.4%) and Days , (↑ 16%) as compared with controls. In the Phase II study, significantly reduced in mean feed consumption in ♂ & ♀ given 600 (♂: ↓ 21%; ♀: ↓ 69%) or 800 mg/kg (♂: ↓ 56%; ♀: ↓ 53%-69%) of SC-59046 was noteworthy.
- Clinical Laboratory Pathology - There were some statistical significant but biological insignificant changes (slightly ↓ RBC with slightly ↑ MCV and MCH) in hematology parameters identified in the treatment groups during Phase I study. Treatment related significant changes in clinical chemistry parameters are presented in the following table.

| Group | TBA | | Urea | | Chol | | ALT | |
|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| **Phase I Study** | | | | | | | | |
| SC-58635 (100→800 mg/kg) | ↑ (1.5x) | | | | | ↑ (1.3x) | | |
| SC-59046 (100→800 mg/kg) | ↑ (1.4x) | ↑ (1.4x) | | | | ↑ (1.7x) | | |
| **Phase II Study** | | | | | | | | |
| SC-58635 (600 mg/kg) | | | | ↑ (2.0x) | | ↑ (2.0x) | | |
| SC-58635 (800 mg/kg) | | | | | | ↑ (1.9x) | | |
| SC-59046 (600 mg/kg) | | ↑ (2.2x) | | | ↑ (1.6x) | | | ↑ (1.5x) |
| SC-59046 (800 mg/kg) | | ↑ (1.2x) | | | ↑ (1.5x) | ↑ (2.0x) | | ↑ (1.5x) |



- Necropsy (Organ Weights, Macro- and Microscopic Pathology) - Cytochrome P-450 content per mg protein was increased in the pooled liver samples from SC-58635 (↑1.8x) & SC-59046 (↑1.5-2.4x) treated animals. Increased mean liver weights (13-36%) and liver/body weight ratios were noted in both SC-58635 and SC-59046 treated animals. No treatment caused macroscopic findings were seen for male or female rats in Phase I study. Two ♀ receiving 800 mg/kg of SC-59046 appeared to be thin. One ♂ from both 600 mg/kg of SC-58635 & SC-59046 groups showed mild to moderate liver enlargement. Slight mild hypertrophy of centrilobular hepatocytes was common finding in Phase I animals receiving treatment.

- PK/TK - Mean plasma levels of SC-58635 & SC-59046 in ♂ & ♀ during the escalating dose phase and tolerance phase were shown in the following table.

| Day | Dose | Time | Plasma SC-58635 (μg/ml) | | Plasma SC-59046 (μg/ml) | |
|---|---|---|---|---|---|---|
| | (mg/kg) | (hr) | ♂ | ♀ | ♂ | ♀ |
| **PHASE I** | | | | | | |
| 3 | 100 | 3 | 5.84 ± 0.47 | 8.00 ± 0.53 | 8.69 ± 0.20 | 10.6 ± 0.6 |
| 6 | 200 | 3 | 6.62 ± 0.16 | 8.40 ± 0.49 | 9.44 ± 0.32 | 10.8 ± 0.9 |
| 9 | 400 | 3 | 7.38 ± 0.70 | 10.1 ± 0.60 | 12.3 ± 0.3 | 14.7 ± 0.3 |
| 12 | 600 | 3 | 8.62 ± 0.73 | 12.5 ± 0.80 | 12.3 ± 0.7 | 16.0 ± 1.4 |
| 15 | 800 | 3 | 7.10 ± 0.51 | 13.9 ± 0.90 | 13.9 ± 1.3 | 20.3 ± 2.7 |
| 16 | 800 | 24 | 5.18 ± 1.31 | 6.28 ± 1.34 | 9.38 ± 2.88 | 18.8 ± 3.7 |
| **PHASE II** | | | | | | |
| 3 | 600 | 3 | 17.8 ± 1.50 | 31.4 ± 10.5 | 23.1 ± 2.1 | 37.1 ± 2.9 |
| 3 | 600 | 24 | 9.09 ± 2.48 | 27.0 ± 16.5 | 19.1 ± 10.0 | 4.64 ± 0.62 |
| 3 | 800 | 3 | 14.8 ± 0.70 | 32.4 ± 3.40 | 38.2 ± 2.4 | 40.7 ± 4.4 |
| 3 | 800 | 24 | 7.88 ± 0.97 | 55.0 ± 7.80 | 16.5 ± 7.4 | 51.8 ± 4.9 |



Plasma levels of SC-58635 & SC-59046 in female rats were much higher than those in male rats. Higher plasma concentrations were observed following administration of drugs to naive rats (Day 3, Phase II) compared to rats received lower dose in an escalating dose schedule (Days 12-15, Phase I) indicating that metabolic eliminations of both compounds were inducible.

2.2.1.4. 4-Week Oral Toxicity Study With SC-58635 In Rats, Document No.: PSA-95C-4261; Date:18-Jan-1995 (Vol. 1.13 -1.14)

Included as an appendix to this report were:

1. Evaluation Of The SC-58635 Plasma Concentration Data From The Four Week Oral Gavage Toxicity Study With SC-58635 In Rats, SA4261 Document No.: MRC-94S-0184; Date: 31-Oct-1994
2. Final Report Amendment No. 1: Evaluation Of The SC-58635 Plasma Concentration Data From The Four Week Oral Gavage Toxicity Study With SC-58635 In Rats, SA4261 (MRC-94S-0184), Document No.: M3194184; Date: 29-Sep-1997
3. Final Report Amendment No. 1: 4-Week Oral Toxicity Study With SC-58635 In Rats Document No.: PSA95C-31-SA4261; Date: 16-May 1995
4. Final Report Amendment No. 2: 4 Week Oral Toxicity Study With SC-58635 In Rats Document No.: PSA95C-32-SA4261; Date: 06-Oct-1997
5. Final Report Amendment No. 3: 4-Week Toxicity Study With SC-58635 In Rats (SA4261), Document No.: P33S4261; Date: 11-Nov-1997

Study Nº: SA4261
Report Nº: PSA-94C-SA4261
Study Aim: To assess the short term toxicity of SC-58635 administered daily by oral gavage to rats for 4 weeks and the reversibility of effects after 4 weeks without treatment
Compound: SC-58635 (Lot Nº GDS-2977-158) in 0.5% methylcellulose and 0.1% Tween 80
Dosage & Route: 20, 40, 80, 400 and 600 mg/kg, 10 ml/kg by oral gavage
Control Vehicle: 0.5% methylcellulose and 0.1% Tween 80
Animals: 66♂ & 66♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR VAF/Plus®, 5 wk of age, weighing g for ♂ and g for ♀; 10 - 15/sex/group for toxicity study and 3/sex/group for PK assessment
Study Location:
Compliance with GLP/QAU: Yes
Study Design: Animal grouping and dosage assignments were listed as following:

| Group | | SC-58635 (mg/kg) | Nº of Animals |
|---|---|---|---|
| TOXICITY STUDY | | | |
| 1 | Control | 0 | 15/sex |
| 2 | Low | | 10/sex |
| 3 | Mid | 80 | 10/sex |
| 4 | Mid-high | | 15/sex |
| 5 | High | | 10/sex |
| PK ASSESSMENT | | | |
| 6 | Mid-high | | 3/sex |
| 7 | High | | 3/sex |



Clinical signs and mortality were monitored twice daily. Body weight measurements (measured 2x before dosing, on the 1st day of treatment and weekly thereafter), food consumption (recorded weekly) estimation, ophthalmological examination, clinical pathology (hematology, clinical chemistries & urinalysis) parameters, and histopathological (macro- and microscopic) examinations were included in the present study. On Day 31 blood samples were collected from animals in groups 6 and 7, prior to dosing and at 2 and 3 hr post dosing.

**Results**:

- Clinical Observations and Mortality - On Day 10, one female in group 5 (600 mg/kg) was found to be moribund and sacrificed. Peritonitis and perforation of jejunum was revealed during the post-mortem pathological examination. On Day 29, one male in group 4 (400 mg/kg) was scarified in a moribund condition and was found to have pyelonephritis at necropsy. One control female was observed to be pale and lethargic, with rough haircoat and labored breath, and subsequently died on Day 31.
- Body Weights, Food Consumption & Ophthalmology - There were no differences in weight gains and food consumption. No noticeable changes could be found during ophthalmology inspection.
- Ophthalmological Examination - No treatment-related changes were noted.
- Clinical Pathology Findings - Lower urine pH, lower $Cl^-$, higher cholesterol, lower albumin and higher globulin were observed for ♀ given 400 or 600 mg/kg during Week 5. But these changes were within normal value ranges.
- Post-mortem Pathology -
  Week 5 Terminal Sacrifice: Slight higher absolute liver weights (11%) for female rats receiving 400 mg/kg and higher liver/body weight ratios for females given 400 or 600 mg/kg were found; but there were no corresponding microscopic findings. There were no test material associated microscopic findings.
  Week 9 Recovery Sacrifice: There were no treatment related changes in terminal body weights. Statistically significant higher absolute thymus and kidney weights, and thymus/body weight and kidney/body weight ratios for female receiving 400 mg/kg and higher absolute epidimides weights for male rate given 400 mg/kg of SC-58635 were noted. No significant macro- and microscopic findings were attributable to the treatment at terminal sacrifice.
- PK Analysis - Mean plasma concentrations (± SEM) of SC-58635 on Day 31 are shown in the following table. Plasma SC-58635 levels were higher in female rats than male rats in dose groups (400 & 600 mg/kg/day). Similar findings were noted in other studies in rats.

| Dose (mg/kg) | Sampling Time (hr) | SC-58635 Concentration (μg/ml) | |
|---|---|---|---|
| | | ♂ | ♀ |
| 400 | 0 | 1.372 ± 0.400 | 5.833 ± 2.576 |
| | 2 | 7.147 ± 1.089 | 12.847 ± 2.926 |
| | 3 | 9.057 ± 1.455 | 17.400 ± 3.523 |
| 600 | 0 | 1.751 ± 0.426 | 10.643 ± 1.010 |
| | 2 | 8.353 ± 0.554 | 17.833 ± 0.953 |
| | 3 | 10.550 ± 0.477 | 21.900 ± 0.458 |



2.2.1.5. 13-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 Document No.: PSA95C-30-SA4346; Date: 11-Jan-1996 (Vol. 1.19-1.21)

Included as an appendix to this report was:
Pharmacokinetics And Metabolism Support For A 13-Week Oral Toxicity Study Of SC-58635 In The Rat, SA4346, Document No.: MRC95S-30-950283; Date: 29-Nov-1995

Report Nº: 700-332, PSA95C-30-SA4346; MRC95C-30-950232 MRC95S-30-950283 (PK & Metabolism)
Study Nº: 700-332 6157-183, SA4346
Study Aim: To identify toxic effects of SC-58635 when administered orally by gavage to rats for at least 13 weeks.
Compound: SC-58635 (Lot Nº 94K014-A4A), SC-58635 (Lot Nº GDS 4404-145,
Vehicle: 0.5% methylcellulose (w/v) + 0.1% Polysorbate 80 (Tween® 80) (w/v) in dist. $H_2O$
Dosage: 0, 20, 80, 400 mg/kg/day, 10 ml/kg po for ≥ 13 weeks
Animals: 388 (194/sex) Sprague-Dawley Crl:CD®BR rats, ~6 wk old.
Study Location:
Study Date: March 16, 1995 - July 14, 1995
Compliance with GLP/QAU: Yes

| Main and Recovery[a] Study | | | | Satellite PK Study | | | |
|---|---|---|---|---|---|---|---|
| Group | Dose (mg/kg/day) | Nº of Animals | | Group | Dose (mg/kg/day) | Nº of Animals | |
| | | ♂ | ♀ | | | ♂ | ♀ |
| 1 | 0 (MC) | 25 | 25 | | | | |
| 2 | | 25 | 25 | 5 | | 18 | 18 |
| 3 | 80 (Mid) | 25 | 25 | 6 | 80 (Mid) | 18 | 18 |
| 4 | | 25 | 25 | 7 | | 18 | 18 |

[a] The recovery group was comprised of 10/sex/group.



Experimental Design: Rats were given SC-58635, 0, 20, 80 or 400 mg/kg/day via oral gavage once daily for at least 13 weeks; dosing continued through the day prior to terminal sacrifice (Days 93/94). Recovery animals were kept without treatment for an additional 4 weeks. Rats in the satellite PK study group received SC-58635 on Days 1, 37, 86 and received nonradiolabeled SC-58635 on other days during the study. Animal and dose group assignments are presented in the above table. The following observations were conducted:

- Mortality and Clinical Signs - 2x/day.
- Body Weight - Day 1, 2x/week for the first 4 weeks of treatment, and 1x/week thereafter.
- Food Consumption - Day -4, and 1x/week thereafter.
- Ophthalmoscopic Examination - pretest and week 13.
- Clinical Laboratory Evaluation - week 6 (5/sex/group) and on the day of sacrifice.
- PK/TK - Blood (12/sex/group, 1 or 2/sex/time point) samples were collected at 0.5, 1, 2, 3, 4, 6, 8, and 24 hr following the ingestion of radiolabeled SC-58635. Each rat was sampled 1x

during the 24-hr period following Day 1 and 2x during the 24-hr period following Days 37 and 86. Fecal and urine samples (3/sex/group) were collected for 7 days after dosing with SC-58635 (Days 1, 37, and 86).

- Necropsy - Days 93/94, the end of the study; the following organs (from scheduled sacrifice animals only) were weighed at necropsy: adrenals, brain (with brainstem), cecum (empty), colon (empty), heart, kidneys, liver, lungs, ovaries, pituitary (postfixation), prostate, spleen, stomach (empty), testes with epididymides, thymus, thyroid with parathyroids (postfixation), uterus; the following tissues (when present) from each main and recovery study animal were preserved in 10% neutral-buffered formalin: adrenals (both), aorta bone marrow (femur and sternum), brain with brainstem (medulla/pons, cerebellar cortex, and cerebral cortex), colon, cecum, rectum, duodenum, jejunum, ileum, esophagus, eyes (both with optic nerve), femur including articular surface, harderian gland, heart, kidneys (both), lesions, liver, lungs (with bronchi), mammary gland with skin, mesenteric lymph node, ovaries (both), pancreas, pituitary, prostate, salivary glands (mandibular), sciatic nerve, seminal vesicle, spinal cord (cervical, mid-thoracic, and lumbar), spleen, stomach, testes with epididymides (both), thigh musculature, thymus, thyroid (parathyroids), tongue, trachea, urinary bladder, uterus with vagina and cervix.

**Results:**

- Mortality & Clinical Observation - Two rats, 1♂ at 20 mg/kg/day and 1♀ at 80 mg/kg/day, died during the study due to blood sampling accident and gavage error, respectively. No other clinical findings were remarkable.
- Body Weight & Food Consumption - Group 4 ♂ had significantly higher mean body weight values during Weeks 4 (Day 26) and 11 and significantly higher mean body weight changes during Weeks 1 (Days 5-8), 4 (Days 22-26), 5, and 10. During the recovery phase, significantly higher mean body weight values were noted for Group 2 males at Weeks 15, 16, 17, and 18. Group 4 ♂ had significant increases in mean food consumption (Weeks 1, 2, 3, 4, 9, 10, 11, and 12) and total food consumption (Weeks 1-13).
- Ophthalmology - No remarkable treatment-related changes were noted.
- Clinical Pathology - One male each at 20 and 80 mg/kg had marked elevations in ALT (524 and 574 U/l, respectively), AST (640 and 815 U/l, respectively), and sorbitol dehydrogenase (SDH) (134 and 136, respectively) at Week 18. Similarly, elevated ALT, AST, and SDH (~2-3x relative to control values) were noted in females at Weeks 6 and/or 14 (1 @ 20, 2 @ 80 and 3 @ 400 mg/kg). Although correlated histopathological lesions were not identified, these changes as results of the administration of the test article could not be ruled out. The urinalysis findings were generally unremarkable and comparable between the groups at Weeks 6, 14, and 18.
- Pathology & Histology - Test article-related histomorphologic alterations were observed in the liver and kidneys at the terminal sacrifice. Minimal to slight change in the liver with centrilobular to midzonal hepatocellular enlargement was seen in both high dose ♂ and ♀ rats. Minimal or slight degeneration of the renal papilla was noted in 1♂ @ 80 mg/kg/day and 3♂ @ 400 mg/kg/day but not in ♀ or rats in recovery phase. There were no treatment-related microscopic changes in the GI tract.
- PK/TK -

  Absorption: SC-58635 was absorbed systemically. Exposure of SC-58635, as measured by AUC and Cmax increased with dose but the increases were not dose-proportional. There were differences in the pharmacokinetics of SC-58635 between male and female rats in that plasma SC-58635 concentrations ($C_{max}$ and AUC) were higher in ♀ rats than ♂ rats. The pharmacokinetics of SC-58635 did not change as a result of repetitive dose administration except in the 400 mg/kg dose group where plasma SC-58635 levels decreased with duration of dosing. The mean PK parameters are shown in the following table.

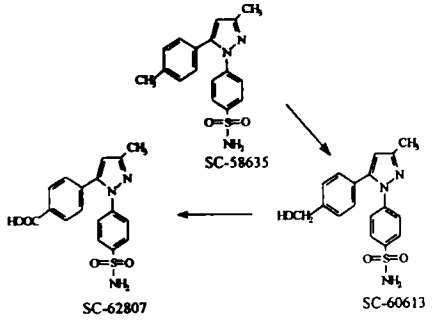
| Day | Dose mg/kg | $T_{max}$ (hr) ♂ | $T_{max}$ (hr) ♀ | $T_{max}$ (hr) ♂ + ♀ | $C_{max}$ (μg/ml) ♂ | $C_{max}$ (μg/ml) ♀ | $C_{max}$ (μg/ml) ♂ + ♀ | $AUC_{0-\infty}$ (μg•hr/ml) ♂ | $AUC_{0-\infty}$ (μg•hr/ml) ♀ | $AUC_{0-\infty}$ (μg•hr/ml) ♂ + ♀ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 20.0 | | | | | | | | | |
| | 80.0 | 6.00 | 6.00 | 6.00 | 3.79 | 5.99 | 4.89 | 42.4 | 83.5 | 62.9 |
| | 400 | | | | | | | | | |
| 42 | 20.0 | | | | | | | | | |
| | 80.0 | 4.00 | 3.00 | 3.00 | 2.58 | 6.86 | 4.53 | 23.4 | 90.3 | 56.8 |
| 91 | | | | | | | | | | |
| | 80.0 | 4.00 | 6.00 | 2.00 | 2.49 | 4.26 | 3.28 | 36.3 | 75.4 | 55.8 |

Radioactivity in Plasma and RBC: Concentrations of radioactivity in the cellular fraction of blood were much higher than in plasma. Following oral administration of 20, 80, and 400 mg/kg of SC-58635 to animals on Day 1 and Weeks 6 and 13, plasma $C_{max}$ occurred from 3 to 8 hours postdose. The plasma $C_{max}$ increased non-proportionally with increasing dose concentrations. Plasma $T_{max}$ increased with dose. The peak levels were higher in females than males. The $T_{max}$ radioactivity in red blood cells occurred from 2 to 8 hours postdose. The $C_{max}$ were higher in ♀ than ♂.

Excretion: The major route of excretion of radioactivity was through the feces. Following administration of 20, 80, and 400 mg/kg of SC-58635 on Day 1 and Weeks 6 and 13, the percentage of the dosed radioactivity excreted in the feces ranged from over the 168-hour collection period with urinary excretion accounting for . As the dose increased, the percentage of dosed radioactivity excreted in the feces generally increased. No changes were observed in the excretion pattern following Day 1 and Weeks 6 and 13 of the dosing regimen. The following table reveals % of radicactive dose in urine, feces, cage rinse, cage wash, cage wipe, and urine wipe at specified intervals postdose for rats following a single oral dose of SC-58635 on Day 1 and Weeks 6 and 13.

| | Dose mg/kg | % of Radioactive Dose: Urine ♂ | Urine ♀ | Feces ♂ | Feces ♀ | Cage Rinse ♂ | Cage Rinse ♀ | Total ♂ | Total ♀ |
|---|---|---|---|---|---|---|---|---|---|
| Day 1 | 20 | | | | | | | | |
| | 80 | 3.34 ± 0.42 | 3.66 ± 1.15 | 81.5 ± 22.5 | 80.9 ± 8.48 | 12.2 ± 17.2 | 10.6 ± 8.2 | 98.0 ± 4.77 | 95.4 ± 1.66 |
| Week 6 | 80 | 4.90 ± 3.67 | 3.42 ± 0.91 | 84.8 ± 2.53 | 83.3 ± 7.87 | 4.80 ± 4.32 | 5.35 ± 2.95 | 95.1 ± 0.31 | 93.5 ± 5.45 |
| Week 13 | 80 | 2.69 ± 1.34 | 3.28 ± 0.65 | 88.5 ± 3.90 | 85.7 ± 6.20 | 1.89 ± 2.26 | 3.34 ± 2.23 | 93.7 ± 3.61 | 94.2 ± 1.04 |

Metabolic Profiles in Blood, Urine and Feces: The majority of the radioactivity circulating in plasma was SC-58635. SC-60613, the hydroxylated metabolite of SC-58635, was also found to circulate in plasma at approximately of plasma radioactivity. There were no detectable differences in distribution of plasma radioactivity between doses or duration of dosing. The majority of the hr urine radioactivity was excreted as SC-62807 (carboxylated metabolite) with no significant differences between sex, dose or duration of dosing. The majority of the fecal radioactivity excreted in the feces was SC-62807 and SC-58635 (hydroxylate metabolite). Mean percentages of dose excreted as



SC-58635, SC-60613 and SC-62807 in feces on Days 1, 42, and 91 are summarized as follows.

| Day | Dose (mg/kg) | % SC-62807 ♂ | % SC-62807 ♀ | % SC-60613 ♂ | % SC-60613 ♀ | % SC-58635 ♂ | % SC-58635 ♀ |
|---|---|---|---|---|---|---|---|
| 1 | 20 | | | | | | |
| | 8 | 31.6 | 26.3 | 1.05 | 1.09 | 47.5 | 50.0 |
| | 400 | | | | | | |
| 42 | 20 | | | | | | |
| | 80 | 33.2 | 28.0 | 1.09 | 2.47 | 41.0 | 50.5 |
| | 400 | | | | | | |
| 91 | 20 | | | | | | |
| | 80 | 19.5 | 22.2 | 0.662 | 2.26 | 67.6 | 60.2 |
| | 400 | | | | | | |

a No peak detected.



**DOG STUDIES**

2.2.1.6. Four Week Oral Capsule Toxicity Of SC-58635 In The Dog With Reversal, Document No: PSA-95S-4260; Date: 18-Jan-1995 (Vol. 1.15-1.16)

Included as an appendix to this report were:

1. Evaluation Of The SC-58635 Plasma Concentration Data From The Four Week Toxicity Study Of SC-58635 In The Dog, SA4260, Document No.: MRC-94S-0185; Date: 17-Nov-1994
2. Report Amendment No. 1: Four-Week Oral Capsule Toxicity Of SC-58635 In The Dog With Reversal Document No.: PSA95S-31-SA4260; Date: 17-May-1995

Study Nº: SA4260
Report Nº: PSA-94S-4260
Study Aim: To evaluate the potential toxic effects of SC-58635 and to assess the reversibility of potential toxic effects
Compound & Dose Form: SC-58553 (Lot Nº 94K014-A1B) in gelatin capsule
Dose & Route: 20, 25, 50, 100 and 250 mg/kg/day in gelatin capsule, oral
Animals: ♂ & ♀ beagle dogs, 9 - 11 months old, weighing kg, 4 or 8/sex/group
Study Location: G.D. Searle, Skokie, IL
Compliance with GLP/QAU: No
Study Design:

| Group | | Dose (mg/kg) | Nº Animals /Sex/Group | Nº Animals/Sex Sacrificed Day 17 | Nº Animals/Sex Sacrificed Days 29-31 |
|---|---|---|---|---|---|
| Toxicology Study | 1 | 0 | 4 (4)* | - | 8 |
| | 2 | 25 | 4 | - | 4 |
| | 3 | 50 | 4 | - | 4 |
| | 4 | 100 | 4 (4)* | 4 | 4 |
| | 5 | 250 | 4 (4)* | 4 | 4 |
| PK Study** | 6 | 25 | 2 | | |
| | 7 | 100 | 2 | | |

* The number in the parenthesis indicating the number of animals were used in the 2 week reversal phase study.
** Animals in group 6 & 7 were treated with [$^{14}$C]SC-58635.



The animals in group 4, 5 and 7 and 4/sex from group 1 were treated 15 doses. The animals in group 2, 3, 6 and the remaining 4/sex from group 1 were treated a minimum of 28 doses. The following parameters were monitored:

- Clinical signs and mortality - 2x/day
- Body Weight - 2x before dosing, Day 1 and 1x/week thereafter.
- Food Consumption - 1x/week.
- Ophthalmological Examination - Days -2 and 28.

- EEG (10 lead: I, II, III, aVR, aVL, aVF, rV2, V2, V4, and V10) - Days -15/-16, 8, and 23.
- Hematology & Clinical Chemistries - Days -6/-7, 2, 9, 10, and 29/30/31.
- Urinalysis - Days-14/-15 and 29/30/31.
- Template Bleeding Time - Days -6/-7, 17, and 29/30/31.
  The whole blood was analyzed for the following parameters: activated partial thromboplastin time and prothrombin time. The following table listed the parameters performed during clinical pathology analysis.

| HEMATOLOGY PARAMETERS | | | URINALYSIS PARAMETERS | |
|---|---|---|---|---|
| White Blood Cells | | MCH | Bilirubin | pH |
| Differential WBC | | MCHC | Glucose | Protein |
| Red Blood Cells | | Mean Platelet Volume | Ketones | Urobilinogen |
| Hemoglobin (Hb) | | Platelets | Occult Blood | Volume |
| Hematocrit (Ht) | | Reticulocytes | Osmolality | Urine Sediment Microscopic Examination |
| MCV | | (Days 16 And 29-31) | | |
| CLINICAL CHEMISTRY PARAMETERS | | | | |
| ALT | Albumin | Creatinine | Potassium | Total Bilirubin |
| Alkaline Phosphatase | | Globulin | Sodium | Total Protein |
| AST | Calcium | Glucose | Sorbitol Dehydrogenase | Triglycerides |
| Chloride | Cholesterol | Inorganic Phosphorus | Total Bile Acids | Urea |

- PK/TK - Non-radioactive Component: Days 1 (Groups 1-5) and 27 (Groups 1-3) at 30 minutes and 1, 1.5, 2, 2.5, 3.5, 5, 7 and 24 hr after dosing; Day 15 (Groups 4 and 5) at 2.5, 3.5 and 24 hr; and Days 29-31 prior to necropsy. Radioactive Component: Days 1 & 28 (Group 6) and Days 1 & 15 (Group 7 animals) at ~30 min, and 1, 1.5, 2, 2.5, 3.5, 5, 7 and 24 hr after administration of the radioactive dose. Feces and urine samples were collected for 7 days after the $^{14}C$ administration.
- Necropsy - Days 17 (interim sacrifice) and 29/30/31. The following listed tissues (when present) or representative samples were collected from all animals and preserved in 10% buffered formalin. The organs (when present) marked with an asterisk were weighed at scheduled necropsy; organs of animals found dead or moribund sacrificed were not weighed. Paired organs were weighed together.

| | | | |
|---|---|---|---|
| Aorta | *Heart | Pancreas | *Stomach |
| *Adrenal Glands (Both) | Intestine, Small (Duodenum, Jejunum, Ileum) | | *Testes (Both) |
| Bone, Femur (Including Articular Surface) | *Intestine, Large (Cecum, Colon) | *Pituitary Gland | *Thymus |
| Bone, Sternum (Including Marrow) | *Kidneys (Both) | *Prostate | *Thyroid Glands** (Both) |
| Bone Marrow Smear (Not Examined) | *Liver | Salivary Gland, Mandibular | Tongue |
| *Brain | *Lungs (Both) | Sciatic Nerve | Trachea |
| *Epididymides (Both) | Lymph Node, Retropharyngeal | Skeletal Muscle | Urinary Bladder |
| Esophagus | Lymph Node, Mesenteric | Skin | *Uterus |
| Eyes (Both) | Mammary Gland (♀ Only) | Spinal Cord (Lumbar) | Vagina |
| Gallbladder | *Ovaries (Both) | *Spleen | Lesions |

**The parathyroids were weighed with the thyroids and examined microscopically if they were included in the thyroid sections.

**Results:**

- Clinical Observation and Mortality - One ♂ & ♀ dogs dosed at 25 mg/kg had black stool during on Days 18 & 19. One ♂ & ♀ dogs receiving 50 mg/kg exhibited black stool during Week 2. **All animals in group 4 & 5 had black stool beginning on Day 5, and pale gums starting on Day 9; these clinical signs persisted throughout the treatment period.** No deaths were seen in Groups 1 and 2. One ♀ receiving 250 mg/kg died on Day 12 as a result of a perforated pyloric ulcer with secondary fibrinous peritonitis. Five animals (1♂ @ 50 mg/kg, 2♂ & 1♀ @ 100 mg/kg, and 1♂ @ 250 mg/kg) were sacrificed in a moribund condition between Days 11 and 14 with clinical signs of black stool; pale gums; difficulty in standing; lateral recumbency; thin appearance; reduced activity; cold to touch; tremors/shivering; stool with white/tan pieces; watery stool; and mucoid stool. One ♂ (250 mg/kg) in reversal phase was also sacrificed on Day

23 (Day 7 of the reversal phase). The following table lists the incidence of mortality including dogs sacrificed at moribund and the numbers of dogs sacrificed at different stages.

| Fate | Study Day | 0 mg/kg | | 25 mg/kg | | 50 mg/kg | | 100 mg/kg | | 250 mg/kg | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Found Dead | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Moribund | 11-14 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 0 |
| Interim Sacrifice | 17 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 4 | 3 | 3 |
| Terminal Sacrifice | 29-31 | 8 | 8 | 4 | 4 | 3 | 4 | 3[a] | 4[a] | 3[a] | 4[a] |

[a] These dogs were dosed with SC-58635 for 15 days and had a 2-week recovery phase.

- Body Weight and Food Consumption - There were no significant differences in mean body weight changes in groups treated with 25 and 50 mg/kg. There was a significant decrease (11.1%) in mean body weight for ♂ @ 250 during week 3. Significant weight losses were noted in ♂ @ 100 and 250 mg/kg during Week 2 with values of 0.3 and 0.7 kg, respectively. On Day 28 (during reversal phase), significant increased in weight gains (0.5 kg) were seen in ♂ & ♀ in the 250 mg/kg reversal group. Mean food consumption was decreased significantly during week 2 for animals @ 250 mg/kg (♂: ↓54.1%; ♀: ↓35.7%). Contrarily, during Week 4, dogs @ 250 mg/kg had increased food consumption by 36.2% (♂) to 51.1% (♀). There was no changes in rectal temperature.
- Ophthalmological Examination & EEG - No ocular abnormalities were noted during week 4. EEG showed no cardiac disorders during Weeks 2 & 4.
- Clinical Pathology - Normal buccal mucosal bleeding times were seen in all animals. There were no changes in clinical pathology parameters in animals receiving 25 mg/kg treatment. Significant and dose-related changes in the values of clinical parameters were seen in animals given 50, 100 and 250 mg/kg. Most of these changes were secondary to intestinal bleeding. **Most notable changes were the progressive and dose-associated ↓ in RBC counts (↓9-23%), hematocrit (↓9-24%), Hb (↓23-32%) and serum proteins (panhypoproteinemia) (albumin: ↓31-54%; globulin: ↓23-26%).** Low serum calcium (↓~20% but within lower normal limit values), higher WBC counts (↑1.7-2x) with higher absolute PMN counts (↑~2x) were also observed. No treatment caused changes in urinalysis parameters.
- Gross Pathology -
  Unscheduled Sacrifices: GI (pylorus, jejunum, distal duodenum and proximal ilum) ulcers/erosions with or without diffuse fibrinosis peritonitis and moderate acute multifocal medullary (papillary) necrosis (1♂ @ 50 mg/kg) were major pathological findings in the animals that died or were sacrificed moribund during Days 11-14. One ♂ @ 250 mg/kg was sacrificed at moribund on Day 23, (Day 7 of the reversal phase of the study) with gross findings of a small focal pyloric ulcer (6 mm in diameter) and numerous ulcers in the mid duodenum, jejunum, and proximal ileum. Other macroscopic observations included interdigital pyoderma (1♂ @ 50 and 2♂ @ 100 mg/kg) and focal areas of subcutaneous inflammation (cellulitis) with necrosis and abscessation in the caudal-ventral neck (2♂ @ 100 and 1♂ @ 250 mg/kg). The sponsor concluded that these cutaneous inflammatory processes were not associated with administration of the test article. **Interdigital pyoderma is a common bacterial infection of the skin of the feet of short-hair breeds of dogs[1]. But, it is seldom seen in the dogs maintained in the experiment control enviroment settings[2]. Therefore, the review pharmacologist does not concur with this conclusion as similar findings of cutaneous lesions were observed in dogs treated with other COX-2 inhibitors[3]. Although these observations occured at low**

1 Muller G.H., Kirk R.W, 1976. Interdigital Pyoderma (Interdigital "Cysts"). Small Animal Dermatology. pp:253-255. W.B. Saunders Co., Philadelphia, PA..

2 Personal experience.

3 [redacted]

**incidence and not appeared to be dose-dependent in the present study, test-article caused toxicity through the mechanism by inhibiting phagocytic cell functions could not be ruled out.**

Interim Sacrifices: A total of 13 dogs (100 mg/kg: 3 ♂ & 4♀; 250 mg/kg: 3♂ & 3♀) were sacrificed on Day 17. Major GI lesions included: pyloric ulcers (1♂ & 1♀ @ 250 mg/kg), segmental intestinal erosions and ulcers ) (100 mg/kg: 2/3♂ & 4/4♀; 250 mg/kg: 3/3♂ & 3/3♀). Commonly, the jejunum was most affected with lesser involvement of the distal duodenum and proximal ileum. Other pathological changes identified were blood in colonic contents (1♂ & 2♀ @ 100 mg/kg and 1♀ @ 250 mg/kg), mild bilateral renal papillary necrosis (1♀ @ 100 mg/kg), moderate splenic enlargement (1♀ @ 100 mg/kg and 1♂ @ 250 mg/kg), ascites and hydrothorax (25-100 ml) secondary to hypoalbuminemia (2♀ @ 100 mg/kg and 1♀ @ 250 mg/kg), and interdigital pyoderma (1♂ @ 100 mg/kg).

Recovery Sacrifices (Groups 4 & 5): Recovery dogs in Groups 4 (3♂ & 4♀) and 5 (3♂ & 4♀) were dosed with SC-58635 for 15 days with a 2-week recovery phase and were necropsied on Days 29-31. Three to 15 small chronic (healing) jejunal ulcers (0.25-0.50 cm in diameter) were identified in 2♂ @ 100 mg/kg and 1♀ @ 250 mg/kg group.

| Macroscopic Observations | 0 | | 25 | | 50 | | 100[a] | | 250 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| Stomach (Pylorus) - Ulcer/Erosion | | | | | 1 | | 1 | 1 | 3 | 2 |
| Small Intestine - Ulcer/Erosion | | | | | 3 | 1 | 6 | 4 | 5 | 5 |
| Large Intestine - Blood in Contents | | | | | 1 | | 2 | 3 | | 1 |
| Kidney- Papillary Necrosis | | | | | 1 | | | | | |
| Skin- Interdigital Pyoderma | | | | | 1 | | 2 | | | 1 |
| Subcutis Abscess - Caudal Ventral Neck | | | | | | | 2 | 1 | 1 | |
| Asites (75-100 ml) | | | | | | | | 2 | | 1 |
| Hydrothorax/Hydropericardium | | | | | | | | 1 | | 1 |

[a] One Group 7 (PK) ♀ dog sacrificed at moribund on Day 12 was included in the Macroscopic analysis.

- Microscopic Findings - There were no treatment-related microscopic findings in dogs given 25 mg/kg of SC-58635 for ≥28 days. The predominant treatment-caused microscopic lesions limited to the GI tract and were characterized by pyloric ulceration, segmental intestinal ulceration, multifocal blunting areas of villus with hyperemia, severe diffuse fibrinopurulent peritonitis (fibrinous inflammation of mesentery and serosa of most abdominal organs (liver, pancreas, urinary bladder, spleen, kidney, large and small intestines). Bone marrow hyperplasia and extramedullary hematopoiesis in the spleen and occasionally the liver were identified in several unscheduled sacrificed dogs, an indicative of regenerative hematopoiesis. There were lesions seen in the brain were characterized as slight→mild chronic multifocal periventricular and perivascular and/or subependymal infiltrates of lymphocytes and macrophages with fewer plasma cells. These changes were seen slightly more frequent in the SC-58635-treated dogs. **Theses pathological changes with perivascular/periventricular lymphocytic infiltrate in brain are often seen in dogs with viral infection such as canine distemper. Data from a rat study (See 1.5.17; Document Nº BRD97D1852) implied that SC-58635 could pass blood-brain-barrier (BBB) and rapidly distribute into CNS tissues as the levels of SC-58635 in CNS were higher than blood following an oral administration of 10 mg/kg. Therefore, the observations of theses changes may be attributable to drug-caused toxicity. It would require additional study to distinguish whether such lesions are drug-induced or due to underlying viral inflammatory diseases of the CNS or other causes.** The incidence of major microscopic observations are shown in the following table.